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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.

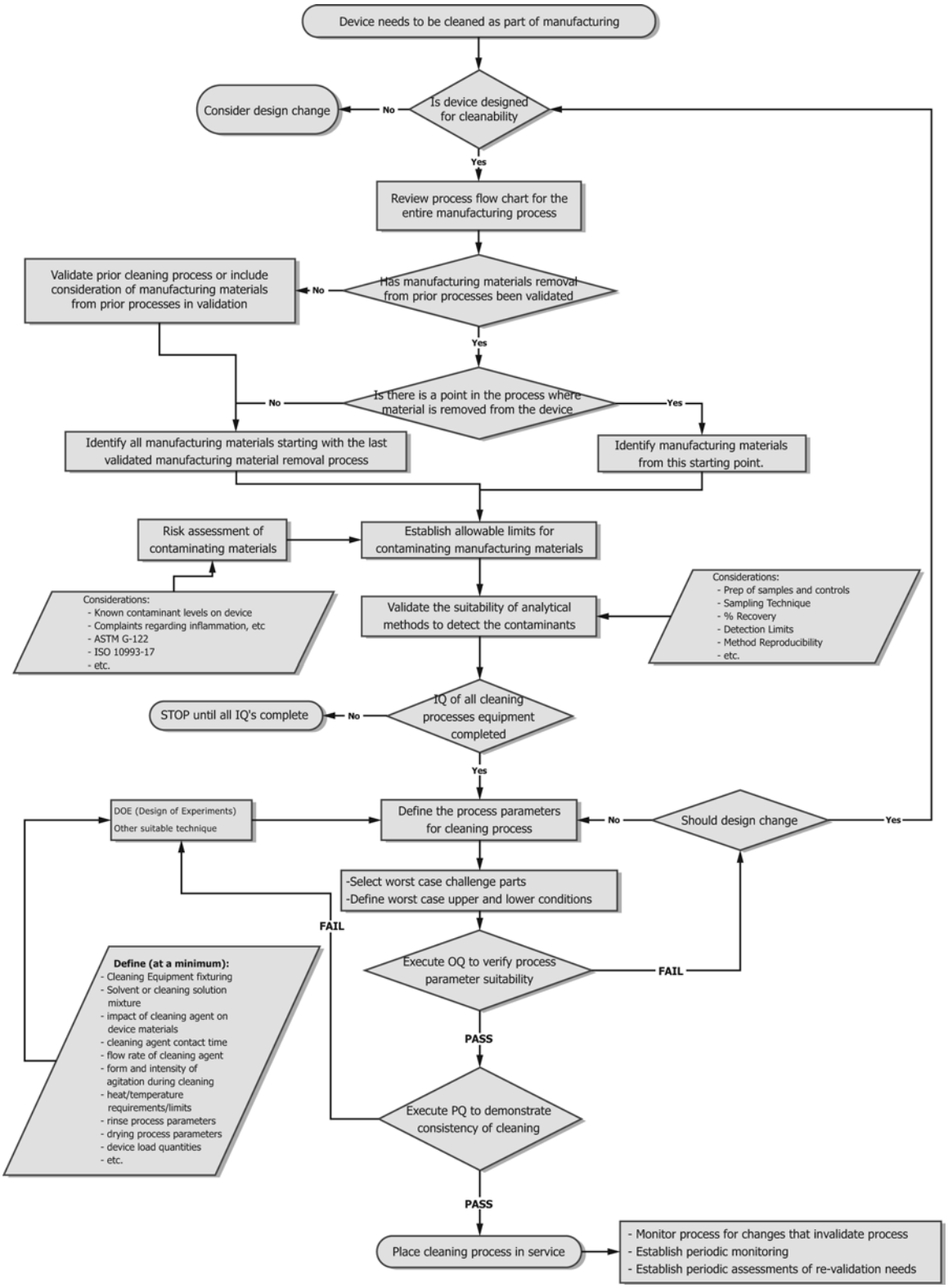

FIG. 1 Process Flow for a Cleaning Validation

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

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.

7.4.3.4 For manufacturing materials that do not have 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> provide guidance on 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.

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 to in-process cleaning operations to minimize the carryover to subsequent operations. See ANSI/AAMI ST72, USP <87> and USP <88> for guidance on methods to evaluate biological contamination.

7.4.6 Note that there are conditions and cleaning parameters in which the cleaning 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 be demonstrated to adequately detect the residues of concern at or preferably below the acceptable limits. Additionally, adequate recovery should 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" or "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 times the standard deviation of the blank.

8.2.1.1 For instrumental methods, this limit is often considered to be 3 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 calculated from the regression curve:

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

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

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

8.2.3 For instrumental methods, this is often considered to be 10 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. Using this method the LOQ can calculated from the regression curve:

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

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".

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

8.4 If levels of contamination or residual 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), 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 E2857, USP <1225>, and ICH Q2 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% recovery) they can be recovered.

NOTE 1—ASTM F2459 requires 75% recovery on the gravimetric analysis.

8.7 Inspection processes that only yield a pass/fail result cannot be qualified using standard Repeatability and 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 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.

8.9 *Specific Analytical Methods:*

8.9.1 Specific analytical methods are those which measure a specific residue in the presence of expected interferences.

8.9.2 The advantage of a specific analytical method is that it provides specific measurements of the major residue of concern.

8.9.3 Examples of methods that can be specific are:

8.9.3.1 Gas Chromatography with a Mass Spectrometer Detector (GC/MS),

8.9.3.2 Infrared Spectroscopy, including micro-Fourier Transform Infra-Red (FTIR) Spectroscopy,

8.9.3.3 High Pressure Liquid Chromatography (HPLC),

8.9.3.4 Enzyme-linked Immunosorbent Assay (ELISA) assays, and

8.9.3.5 Gel Electrophoresis (sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE)).

8.10 *Non-Specific Analytical Methods:*

8.10.1 There are several non-specific analytical methods that can be useful for detecting the presence of residues or contaminants.

8.10.2 Non-specific methods measure a general property which could be a combination of residues or contaminants.

8.10.3 The advantage of non-specific methods is that it provides a measurements of total levels of residues or contaminants of a given type, organic, inorganic, biologic, particulate, etc.

8.10.4 Examples of methods that are not specific to a particular contaminant include:

8.10.4.1 Gravimetric Analysis,

8.10.4.2 Total Organic Carbon (TOC),

8.10.4.3 Total Protein,

8.10.4.4 Conductivity,

8.10.4.5 Visual Inspection, and

8.10.4.6 Water contact angle.

8.11 *Microbiological Test Methods:*

8.11.1 Control of the bioburden and endotoxin in a cleaning process is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary sterility assurance. Methods to evaluate residual bioburden include ANSI/AAMI ST72, USP <85>, and ANSI/AAMI/ISO 11737-1.

8.11.2 Depending on the medical device, both bioburden and endotoxin are monitored and controlled during the manufacturing and cleaning processes.

8.12 *Biocompatibility Testing:*

8.12.1 Biocompatibility testing (e.g., cytotoxicity as described in ISO 10993-05) can be appropriate for determining if the output of a cleaning process meets its specified requirements.

8.13 *Sampling:*

8.13.1 Preparation of samples of residues and contaminants for cleaning validation testing for analytical testing is as critical as the test itself. If a sample is prepared inappropriately, the result will also not be appropriate.

8.13.2 The analytical method validation should include the sampling technique as a confounding factor for interference determination and for recovery studies.

8.13.3 *Direct Surface Sampling:*

8.13.3.1 Direct surface sampling using surface analytical techniques like Photoelectron Spectroscopy (PES), Time of Flight Secondary Ion Mass Spectroscopy (TOF-SIMS), Energy Dispersive Spectroscopy (EDS) and micro-FT-IR can provide direct sampling of surfaces. These techniques can have the advantage that they provide immediate results about specific sites on surfaces. They also can provide direct evidence at the worst-case locations or at the best-case locations. While there are no specific recovery issues, direct surface sampling can have the disadvantage that the techniques may not provide an overall picture of the device. It may lead to erroneous conclusions because of sampling bias. Direct surface sampling is dependent on how and where sampling sites are chosen. Imaging techniques, based on direct surface sampling, can also provide an overall view of the relative distributions of residues and contaminants. Each of these techniques has technique-specific requirements for the sample surface such as a requirement for surface flatness, the ability to withstand high vacuum, depth of penetration, and access to the desired sample location due to equipment limitations. The costs associated with these techniques can also be a limitation.

8.13.4 Swab sampling is also a direct surface sampling technique that is reasonably cost-effective. It provides information about the specific sites selected and swabbed. Swabbing protocols that reduce swab sampling bias should be developed. A limitation of swab sampling is that the swab should “release” the residue or contaminant. The ability of the swab to release the residue should be considered in the recovery study. There are also potential interferences from the swab (based on swab material composition) that should be considered and minimized. Swabbing is a manual operation so procedures should be established to develop sampling consistency.

8.13.5 Rinse sampling and extraction by immersion involves the use of a solvent to contact all surfaces of a sampled item to quantitatively remove the residue or contaminant. The solvent can be water, water-based or organic, depending on the relative solubility of the residue or contaminant and the composition of the medical device. Different solvents can be used to evaluate residues of different solubility on the same sample groups.

NOTE 2—If a sample is used for one rinse or extraction, the exact same part should not be used again with a different solvent.

Sampling and extraction can be assisted by ultrasonic agitation, reflux, bubbling, or with heat. The residue in the collected rinse solution is measured using either a specific or non-specific method. Particle collection and quantification can occur per ASTM F2459.

8.13.5.1 Rinse sampling has the advantage that it reaches often inaccessible locations on the device or product. It provides an average or overall picture of the cleanliness of the device or product.

8.13.5.2 The disadvantage of rinse sampling is that it is dependent on the solubility of the residue. For reasons of cost

and time, there can be a tendency to use only a single solvent. Multiple solvent rinses, using solvents of differing solubility, can provide a more complete picture of the cleanliness of the device or product because other residues, having different polarities, can be identified. It is essential that solvent(s) which are verified to be capable of dissolving all known residues without affecting the medical device be chosen, as the results could lead to an false positive.

8.13.5.3 The method validations should consider the impact of volume reductions (evaporation of solvent to increase the concentration of the analyte) of the extracting solvents to ensure that the concentration of the extracting solvent does not contribute to the result. Documentation of extraction process should include specifying the appropriate quantity and the appropriate quality of water and/or one or more of the correct quality of extraction solvent(s). The extraction process (including temperature, force, and time) should also be developed and documented so that the residue is identifiable. In other words, the residue cannot be swamped by artifactual interferences from the extraction media or the extraction process. Appropriate controls to establish the suitability of the solvent to extract the residue should be evaluated and considered in a recovery study. Potential interferences from the solvent should be considered and minimized. Both positive (recovery) and negative controls should be specified.

8.13.5.4 In some instances, a volatile residue should be considered. In such an instance, rather than an extraction in a liquid, extraction in the vapor phase combined with head-space gas chromatography (GC) may be appropriate.

8.13.5.5 Certain types of devices (e.g., porous devices and some coatings) may not be suitable for surface detections methods.

8.13.5.6 There are available standards for some rinse sampling techniques including Practice F619 and Test Method F2459.

9. Sample Size

9.1 The sample size required to reach a justifiable conclusion for a given cleaning validation is dependent on a valid statistical approach, the analytical technique, the variability of the analytical technique, and the desired outcome of the test. Factors that should be considered include the following:

9.1.1 Will the results of the process evaluation be compared to an existing process?

9.1.2 Will the results be used to develop a process?

9.1.3 Will the results be used to qualify a new process?

9.2 In order to give some guidance on how sample sizes can be determined for a cleaning validation, some examples of approaches to establish sample size are provided in Appendix X2 and the validation example.

9.3 Note that the sample size justification and statistical procedures used to analyze the data should be based on sound scientific principles and should be suitable for reaching an appropriate and justifiable conclusion.

9.4 If a statistically significant sample size is overly burdensome, a nonstatistically-based sample size may be justified.

9.5 Questions that should be considered and resolved prior to writing the cleaning validation plan include:

Questions	If Yes	If No
Is the process controllable and adequately defined?	The process is ready for validation	Then define the process and establish approaches to control the process
If the process is not controllable and adequately defined, is there a need to develop a new process such that it is controllable?	Develop the new process and validate	Verify the output of the process
If the process will be fully verified, is the verification cost-effective?	Verify the output of the process	Consider validating the process
Has the process been defined?	Begin planning the validation	Define the process
Has a process flow chart been developed?	Define the inputs and outputs of the process	Develop the flow chart
Identified process inputs (raw material, manufacturing materials, subcomponents, fixtures, tooling, etc.)?	Consider the process parameter specifications	Identify all manufacturing materials, cleaning agents, fixtures, etc.
Manufacturing materials • Blast grit • Oils • Polishing compound properties • Coolant types • Cleaning Solvents • Tooling and fixture materials • Masking materials • Water/Air quality • Other variables as deemed critical	Address these items in the risk analysis and in the validation plan	
Has the step at which inputs enter process been dentified?	Address these items in the validation plan	Complete the process flow chart to include the inputs

Questions	If Yes	If No
Have process parameter specifications (including limits) been defined?	Use the process parameters in the OQ	Develop designs of experiments to determine appropriate process parameters
Manufacturing processes variables (from Flow Chart) • Blasting • Polishing • Machining • Mass Finishing • Annealing • Dwell times • Drying • Other variables as deemed critical	Address these items in the validation plan	Consider the impact of each of the process variables with an appropriate design of experiments to establish process parameters
Have the necessary process controls been identified?	Validate the process controls	Develop appropriate process control methods
Has the manufacturing process rework that would impact the output of this process been defined?	Verify that rework processes are included in the validation	Consider rework in process flow and impact on validation
Has all equipment used in the process been identified?	Consider impact through risk analysis and consider in validation plan	Identify all equipment and include in flow chart and validation planning
Have all utilities required for the process been identified?	Include in IQ	Verify all utility requirements
Has all software used in the process been identified?	Include in IQ	Verify all utility requirements
Is all equipment suitable for use?	Verify with IQ	Consider repair or replacement and re-execute the IQ
Has all software needed for the process been validated or will be validated ?	Include in validation plan or validation plan justification	Include in validation plan
Is the detailed process flow chart complete?	Plan validation activities	Do not begin planning validation until complete
Has the Process Failure Mode and Effects Analysis (PFMEA) been completed for the process?	Include in Plan validation activities	Do not begin planning validation until complete
Has the risk to the patient or the risk to the downstream process been determined?	Then the result of an evaluation could be used as part of the risk analysis	Then the impact on downstream processes should be evaluated to establish acceptable cleaning process limits
Does the cleanliness of the component as it exits the cleaning process have an impact on a downstream process?	Then the impact on downstream processes should be evaluated to establish acceptable cleaning process limits	Then the acceptable cleaning process limits can determined by some other factor
Does the cleanliness of the component impact downstream yields?	Then the impact on downstream processes should be evaluated to establish acceptable cleaning process limits	Document justification in validation planning activities
Does the cleanliness of the component or medical device at this stage in the manufacturing process have an impact on the performance of the medical device, or instrument, when used by the customer?	Then the impact on performance should be evaluated to establish acceptable cleaning process limits	Document justification in validation planning activities
Is there a point in the process where manufacturing material removal from prior processes has been validated?	Identify all manufacturing materials starting at this point	Identify all manufacturing materials from prior processes
Are there any Corrective Actions/Preventative Actions (CAPA's) associated with the process?	Consider failure mode in the process	Document justification in validation planning activities
Have acceptance criteria for contaminating manufacturing materials been established?	Identify suitability of analytical methods	Consider PFMEA
Is there a clinical history for the medical device?	Then the result of an evaluation could be used as part of the risk analysis	Then base the risk analysis on preclinical data only

Questions	If Yes	If No
Have there been complaints or adverse events associated with inflammatory responses or infection associated with the medical device?	Can be used in the risk analysis and sample size selection	Sample size selection is based on risk to patient
Have there been complaints or adverse events that involved a failure or malfunction of the device that can be associated with a cleaning operation?	Then the validation should include any corrective actions that result from the root cause analysis	Determine if FMEA document revision is necessary
Have the process outputs (product requirements) for each step been defined?	Then the OQ can be executed	They should be defined prior to executing the OQ
Have all test methods used to verify product requirements are met been identified?	Validate their suitability	Test methods should be identified and validated before OQ or PQ
All test method validations completed?	Use for cleaning validation	Validate the methods before OQ or PQ
Has a process validation plan been developed?	Execute plan	Develop plan based on PFMEA and process flow chart
Has the process scope been identified?	Take scope into account when preparing OQ and PQ	Determine the scope of the validation plan
Has the product scope been identified?	Take scope into account when preparing OQ and PQ	Determine the scope of the validation plan
Have appropriate sampling plans been established or justified?	No additional action required	Develop appropriate sampling plan based on PFMEA and process needs
Has it been determine if multiple pieces of equipment are required?	Validate equipment or just not validating	Determine if multiple pieces of equipment are required
Have worst-case process conditions based on process parameter specifications (including downstream rework and/or reprocessing) been identified?	Use for OQ	Identify using design of experiments or similar
Is the worst case product identified?	Use for OQ	Identify using design of experiments or similar
Have the sampling plans for all process requirements for OQ been determined?	Use for OQ	Identify using design of experiments or similar
Have all anticipated sources of variation in the process been identified?	Use for OQ	Identify using design of experiments or similar
Has it been verified that the resolution of the inspection method of all product requirements is adequate?	Use for OQ	Verify prior to starting OQ or PQ
Has it been verified that the resolution of the equipment used to measure all process parameters is adequate?	Use for OQ	Verify prior to starting OQ or PQ
Does the sampling plan include all anticipated sources of variation?	Use for OQ	Consult the PFMEA
Has the sampling plan for all product requirements for PQ determined?	Use for PQ	Consider process risk or justify
Does the sampling plan include all pieces of equipment?	Use for PQ	Justify or reconsider sampling plan
Is an ongoing monitoring and control plan defined?	No further action required	Consider PFMEA
Is the revalidation plan defined?	No further action required	Consider PFMEA

APPENDIXES

(Nonmandatory Information)

X1. A PERSPECTIVE ON "HOW CLEAN IS CLEAN ENOUGH?"

INTRODUCTION

Each manufacturer of medical devices has the responsibility to remove manufacturing materials to ensure that they are removed or limited to an amount that does not adversely affect the device's quality. There is no specific standard or definition that can be attributed to "How Clean is Clean Enough?" because it depends on the needs of the product and it should be determined by the manufacturer of the device. The manufacturer's rationale for the residue limits established ("How Clean is Clean Enough?") should be practical, achievable, and verifiable, and should be based on the manufacturer's knowledge of the materials and processes involved.

Visual inspection of incoming cleaning agents can often help determine if the material is contaminated. Given the number of variables involved, there can be instances where the cleaning chemistry has changed even though vendor certifications are acceptable. Therefore, the importance of observation and visual inspection is essential. A formal visual inspection should be part of incoming QC. Aspects may include color, clarity, or perceived changes such as odor. For example, in a complex mixture (such as in many aqueous cleaning agents), a change in odor could indicate a change in formulation or the unanticipated addition of a masking odor. In addition, in solvents or solvent blends, a change in color or clarity could indicate a breakdown in the cleaning agent that may have resulted from formulation changes or reaction with storage or transfer materials.

Changes in cleaning agents may be subtle and may not become apparent until the actual production process. Therefore, a level of judicious wariness on the part of technicians is essential and they should be considered as part of the quality management system. Instructions to report unusual changes in cleaning performance, or unexpected reactivity should be part of the assembly instructions as well as part of initial and ongoing training.

While visual determination of cleanliness is highly subjective, it can be somewhat systematized.[4] Therefore, in addition to inspection of incoming cleaning agents, it is suggested that a program to review the visual appearance of equipment and peripherals as received. Similarly, the appearance of equipment and peripherals should be monitored periodically.

[4] Forsyth et al, "Ruggedness of Visible Residue Limits for Cleaning-Part III: Visible Residue Limits for Different Materials of Construction," *Pharmaceutical Technology*, October, 2013.

X1.1 *Example of an Approach to a Cleaning Validation*:

X1.1.1 This description of a validation approach is an example of a process that could be used as a basis for developing an appropriate and justifiable cleaning validation plan. It is not all encompassing. The details of the approach should be established to meet the requirements for the product or process and address risks identified during process development. Before executing this validation, verify that all equipment used in the process has been adequately qualified (IQ) and that the process has been qualified (OQ). The process qualification (PQ) to demonstrate consistency of the process, should be completed before the cleaning process can be considered validated.

X1.2 *Process Development*:

X1.2.1 Prepare the test residue or contaminant that is appropriate for the device or product that is being tested.

X1.2.2 Determine the method (assay) to be used to recover and test the residue or contaminant and validate the method.

X1.2.3 Apply the test, or actual manufacturing, residue or contaminant to 3 lots of worst-case devices using a technique that mimics in-use processes.

X1.2.4 Allow the test residue or process contaminant residue to dry under environmental conditions deemed appropriate (e.g., the drying cycle of an automated washing device). The drying times should include a realistic minimum and extended times that reflect worst-case in-use process hold or dwell conditions for the device.

X1.2.5 Process the set of contaminated devices using the cleaning process to be validated at nominal cleaning process conditions. The sample size should be statistically valid for each variable test or defined by a standard. For ASTM F2459 gravimetric methods, this is normally six to ten samples per

variable test. Other more precise instrumental methods may yield lower sample sizes. See Appendix X2 for examples.

X1.2.6 Analyze the residual or contaminant levels on the 3 lots of devices.

X1.2.7 If samples have residual levels that are below the LOD or LOQ, then the limits of detection or of quantitation for the method should be identified in the reporting of the results.

NOTE X1.1—If it is not possible to apply specific or known manufacturing materials, due to a complex matrix of contact materials, run the worst-case product or products through the manufacturing process and represent process variability by gathering at least three lots. Multiple methods that address the full range of contaminants would need to be used to have adequate confidence in residue or contaminant removal.

X1.2.8 PQ processing should also analyze three lots of parts taken at various times in the cleaning cycle between tank cleanouts and processed on different shifts/days/weeks in order to capture all process variation. At least one of the lots should be taken near the end of the tank clean-out cycle. Implants need not be worst case but should represent the part families cleaned in the cleaning process being validated. Each PQ lot shall have a statistically valid number of samples and be analyzed for statistical confidence and capability independently of other PQ lots.

X1.3 *Report*:

X1.3.1 Reporting requirements are established by the organization performing the cleaning validation.

X1.3.2 The practice for reporting and assessment of residues on single use implants provided by ASTM F2847 can also provide a template for reporting the result of the cleaning validation.

X2. APPROACHES TO SAMPLE SIZE SELECTION

X2.1 Insufficient sample size may lead to erroneous conclusions. The sample size for any test should be established in the validation plan, and should be based on the criticality of the process.

X2.2 There are multiple ways of determining sample size for cleaning validation, using a variety of statistical models. Some example methods are shown below. Any approach to determining the appropriate sample size should be accompanied by a rationale.

X2.2.1 *Variable Data* based on tolerance interval (Parametric, One-sided, Standard Deviation Unknown):

X2.2.1.1 *Objective*—To determine the sample size for medical device cleaning validation protocols based on the limit value and estimates of the average and standard deviation.

X2.2.1.2 *Definition*—A one-sided interval, value, such that a stated proportion, P, of the population will lie below the value with a specified confidence 1-α.

X2.2.1.3 *Assumed*—The data are an independent random sample from a single population.

(1) The data are normally distributed.

(2) The true mean of the population is *not known*.

(3) The standard deviation of the population is *not known*.

NOTE X2.1—Variables:

α is the risk of decision or significance level.

γ = 1-α, is the confidence level.

P is the proportion of the population.

X2.2.1.4 *Procedure:*

(1) Identify the data to be used for estimates of average (X_e) and standard deviation (S_e), and determine X_e and S_e.

(2) Identify the selected limit value L (using whatever criteria the firm is using).

(3) The significance level α is 0.05 and the confidence level γ is 95% [or γ = 100(1-α)%].

(4) Determine the factor K_e based on the formula:

$$K_e = (L - X_e)/S_e$$

(5) Refer to Table X2.1, and select a factor K that is at or below the calculated K_e. The sample size n associated with that K value from Table X2.1 is the minimum sample size to utilize assuming the values selected for X_e and S_e are conservative values (that is, the actual average is lower and the actual standard deviation is lower). Manufacturers may include a "safety" factor by estimating average and standard deviation higher than expected or by selecting a value for n larger than the minimum value of n associated with K_e. This is to prevent false failures. One technique is to use an upper confidence bound of the process average and standard deviation, however, this may lead to unpractical, large sample sizes when estimates are made using small samples. Selection of X_e and S_e is

TABLE X2.1 *K* Factor as a Function of Sample Size

Sample Size, *n*	*K* Factor, 95%/95%
3	7.656
4	5.145
5	4.202
6	3.707
7	3.399
8	3.188
9	3.031
10	2.911
11	2.815
12	2.736
13	2.670
14	2.614
15	2.566
16	2.523
17	2.486
18	2.453
19	2.423
20	2.396
21	2.371
22	2.350
23	2.329
24	2.309
25	2.292
30	2.220
35	2.166
40	2.126
45	2.092
50	2.065

balanced between the cost of sampling more parts than needed versus cost of false process validation failures.

(6) In cases where estimates of X_e and S_e are unknown analysis of cleaning validations has shown a sample size of n=6 for a cleaning process analyzed with gravimetric methods is typically sufficient.

NOTE X2.2—Following collection of data in a cleaning validation protocol, actual values may be evaluated statistically to determine that the sample size is adequate. If the actual mean is X_a and the actual standard deviation is S_a, and the sample size is n, then using the value of K associated with n in Table X2.1, calculate the value at the upper confidence level (95%) as: $X_a + (K)(S_a)$. If the calculated value is below the L, then the sample size is adequate to state "We are 0.95 confident that 95% of the population values will lie below L." There are three possible outcomes:

(a) If the calculated value is below L, then the validation test passes the acceptance criteria. "We are 0.95 confident that 95% of the population values will lie below L."

(b) If the calculated value at 50% confidence 95% of population (K=1.645) is above L, then the validation test fails the acceptance criteria. "We do have a high degree of assurance 95% of the population values will lie below L."

(c) If the calculated value at 95%/95% is above L, but the calculated value for 50%/95% is below L, then the process is good but more samples are needed to demonstrate the confidence required. "The process produces 95% of the population below L, but more sampling is needed to demonstrate a high degree of assurance" If this is the case and additional parts are available add more test parts to the sample and recalculate the upper tolerance limit. If not, create a new sample. To calculate the total number of parts needed, use the mean and standard deviation from the original study and the K factors in Table X2.1 to determine an appropriate sample size.

NOTE X2.3—A conservative estimate of X_e and S_e should be used to prevent false failures. One method is to calculate the upper 95% confidence bound of the mean and standard deviation when calculating sample size.

X2.2.1.5 *References:*

Natrella, Mary G., 1963, 1966, "Experimental Statistics; Handbook 91," NIST, Library of Congress Number: 63-60072.

X2.2.1.6 *Additional Tables:*

Hahn, G. J. and Meeker, W. O., (1991). "Statistical Intervals." John Wiley and Sons, New York, NY.

X2.2.2 *Attribute Testing (pass/fail):*

X2.2.2.1 Sample sizes for attributes may be calculated using the following equation, which is found in *Reliability Statistics*, by Robert A. Dovich.[5] The resulting sample sizes assume no test failures within the sample:

$$n = \frac{\ln(1 - c)}{\ln(q)} \quad \text{(X2.1)}$$

where:

n = the sample size (with no failures),
c = the confidence level (decimalized percentage), and
q = the quality level (yield, decimalized percentage non-defective).

[5] ASQ Quality Press, Milwaukee, 1990.

X2.2.2.2 Table X2.2 provides select results from the equation for C=0, always rounded up to the next integer value to assure an adequate sample.

NOTE X2.4—Other tables can be used to identify appropriate sample sizes for C greater than 0. These tables are also readily calculated using many statistics programs.

X2.2.3 *Variables Testing:*

X2.2.3.1 For a one-sided hypothesis test (assuming that the minimum requirement is a Not Detectable value) where there is a need to detect an increase in the population mean of one standard deviation (any assigned difference can be detected and does not have to be limited to one standard deviation), the following information is required: α, the significance level of the test, and β, the probability of failing to detect a shift of one standard deviation. To control the risk of accepting a false hypothesis, set not only α, the probability of rejecting the null hypothesis when it is true, but also β, the probability of accepting the null hypothesis when in fact the population mean is μ+δ where δ is the maximum allowed error in one sample.

X2.2.3.2 The minimum sample size, N, is shown below for a one sided tests of hypotheses with σ assumed to be known:

$$N = (Z_{1-\alpha} - Z_{1-\beta})^2 \left(\frac{\sigma}{\delta}\right)^2 \quad \text{(X2.2)}$$

X2.2.3.3 The quantities $Z_{1-\alpha}$ and $Z_{1-\beta}$ are the statistics from the normal distribution.

$$N_{test} = Z_{\alpha}^{\,2} \left(\frac{\sigma}{\delta}\right)^2 \quad \text{(X2.3)}$$

where:

N_{test} = number of samples needed for the test,
α = a predetermined, assumed confidence interval,
Z_α = statistic for a normal distribution,
E = error between the specification acceptance value and the true mean, of the population,
σ = historical standard deviation for the test, and
δ = the maximum allowed error of one sample.

X2.2.4 *t-Test Analysis:*

X2.2.4.1 The sample standard deviation, s, and mean, $\bar{x}$, will approach the population (all cleaned samples ever produced) standard deviation, σ, and mean, μ, as the number of tested specimens n increases towards the total population number N.

$$\sigma = \sqrt{\frac{\Sigma(x_i - \mu)^2}{N}}; s = \sqrt{\frac{\Sigma(x_i - \bar{x})^2}{n-1}} \quad \text{(X2.4)}$$

X2.2.4.2 As more samples are taken, the standard deviation in the error between the true mean and the calculated mean is

TABLE X2.2 Sample Size for Attributes

q \ c	0.90	0.95	0.975	0.99	0.999
0.75	9	11	13	17	25
0.80	11	14	17	21	31
0.85	15	19	23	29	43
0.90	22	29	36	44	66
0.925	30	39	48	60	89
0.95	45	59	72	90	135
0.975	91	119	146	182	273
0.99	230	299	368	459	688
0.999	2302	2995	3688	4603	6905

called the standard error of the mean, denoted $\sigma_{\bar{x}}$, with the form (which is based on the population standard deviation):

$$\sigma_{\bar{x}} = \frac{\sigma}{\sqrt{n}}; s_{\bar{x}} = \frac{s}{\sqrt{n}} \quad \text{(X2.5)}$$

X2.2.4.3 Using these computations, an estimate of the sample size that will be required to accurately determine the true average residue remaining on the components within a certain tolerance can be obtained. A confidence interval for the population mean μ can be constructed using the formula:

$$\bar{x} \pm z_c \sigma_{\bar{x}} \quad \text{(X2.6)}$$

X2.2.4.4 However, this discussion assumes that sufficient information is known about the population statistics to determine σ accurately. Simply replacing the population statistics (σ) with the sample statistics (*s*) for a "small" number of specimens may not be sufficient. Normally, one determines the sample size required by using accurate estimates of the underlying population quantities. These values should be obtained either through historical data, or through a pilot study. In this case we propose using a small pilot study to estimate the population values and use these for the sample size calculation. To account for the increased uncertainty by replacing σ with *s*, in Eq X2.7, we recognize that the form of the confidence interval for μ is given by:

$$\bar{x} \pm t_c s_{\bar{x}} \quad \text{(X2.7)}$$

where t_c is the critical value from the *t*-distribution with *df* degrees of freedom, where *df*=*n*-1.

X2.2.4.5 Critical values from a *t*-distribution with given *df* are routinely tabulated and computable in most statistics computer packages. For the same level of confidence (e.g., 95%), the value of t_c for any value of *df* is always larger than the corresponding value of z_c to reflect the extra uncertainty based on using a sample standard deviation instead of the population standard deviation. The formula is used:

$$n = \left(\frac{t_c s}{E}\right)^2 \quad \text{(X2.8)}$$

to determine the minimum sample size *n* required to obtain a confidence interval having a margin of error no larger than *E*, with specified the sample standard deviation s from pilot data.

X2.2.4.6 Values of *E* can be estimated based on weighing resolution of the overall procedure. As t_c depends on *n*, Eq X2.8 needs to be solved iteratively using T-tables.

X2.2.4.7 Following collection of residue levels, the sample size *n* should be re-calculated based on the actual standard deviation computed from the test data. Additionally, the normality of the sample residue distribution should be verified to assure that Eq X2.8 is appropriate.

X2.2.5 Guidance in selection of an appropriate confidence level and quality level is provided by Fig. X2.1.

NOTE X2.5—Fig. X2.1 is provided as a guide for selection of appropriate Quality Levels and Confidence Levels, based on the needs and application of the test. A more detailed analysis can result from using appropriate OC (Operating Characteristic) curves found in several references and statistics programs.

X2.2.5.1 Sample sizes in the dark green zone can be considered highly conservative.

X2.2.5.2 Sample sizes in the light green zone can be considered conservative unless risk of patient harm is severe if failure were to occur.

X2.2.5.3 Sample sizes in the yellow zone are dependent upon the criticality of the decision being made (e.g., if used for final product acceptance or final verification and validation testing that confirms device function or performance). In such cases the influence of Type II error and minimizing its impact to user/patient risk should be considered.

X2.2.5.4 Sample sizes in the orange zone should be evaluated to ensure they are commensurate with risk. These sample sizes may be used when there are technical limitations within

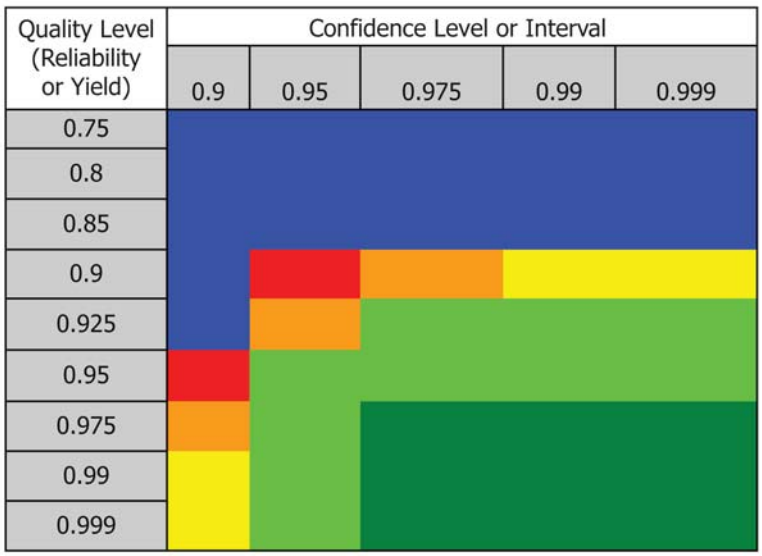

FIG. X2.1 Selection Matrix for Confidence Level and Quality Level

the measurement process, sample size, or number of trials/replicates that cannot be overcome.

X2.2.5.5 Sample sizes in the red zone should only be used in extenuating circumstances where Type II error is unlikely to contribute to user/patient risk. Sample size selections in this zone should not be used for final product acceptance, testing to mitigate an intolerable risk or final verification/validation without other supporting confirmatory studies.

X2.2.5.6 Sample sizes in the blue zone should be used for proof of concept, technical feasibility, characterization or investigative/experimentation purposes and not for the purposes of: final product acceptance, final verification/validation testing, or for testing to mitigate intolerable risk to a tolerable level.

X2.2.5.7 Any of the above sample size selection criteria may be used in conjunction with a sound Design of Experiments where variation is purposefully introduced and studied (targeted testing) to better characterize and understand the impact of boundary conditions as such designs generate even more conservative estimates with regard to a given population.

X2.2.5.8 Other sample size selection criteria may be used if they follow sound scientific principles, are applied appropriately, and are appropriately justified. Regardless of the sample size selection criteria chosen, careful consideration of the following should be undertaken:

(1) Accuracy and precision (uncertainty) of the analytical method,

(2) Statistical confidence of the test chosen with regard to the decision needed, and

(3) How outliers will be identified, analyzed and resolved if encountered.

X3. OTHER CLEANING VALIDATION APPROACHES

X3.1 Cleaning validation approaches that have been developed and documented for other business needs include:

X3.1.1 *Reusable Medical Devices:*

AAMI TIR30:2011 A Compendium of Processes, Materials, Test Methods, and Acceptance Criteria for Cleaning Reusable Medical Devices

X3.1.2 *Parenteral Drug Association:*

Technical Report No. 49: Points to consider for Biotechnology Cleaning Validation

Technical Report No. 29: Points to Consider for Cleaning Validation

X3.1.3 *Pharmaceutical Manufacturing:*

The FDA Guide to Inspections: Validation of Cleaning Process

X3.1.4 *Oxygen-Enriched Systems and Components:*

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

NOTE X3.1—The use of coupons as surrogates may not always reflect the complexity of the medical device design such as long narrow lumens, textured or rough surfaces, etc. Careful consideration of relevance and justification suitability should include the use of coupons in cleaning validations.

ASTM G122 Test Method for Evaluating the Effectiveness of Cleaning Agents

ASTM G131 Practice for Cleaning of Materials and Components by Ultrasonic Techniques

X3.1.5 *Printed Circuit Board Manufacturing:*

IPC-CH-65B: IPC Guidelines for Cleaning of Printed Boards and Assemblies

X3.1.6 *Other References and Handbooks:*

Handbook for Critical Cleaning: Cleaning Agents and Systems (Book 1) and Applications, Processes and Controls (Book 2), Barbara Kanegsberg & Edward, Kanegsberg, ed., CRC/Taylor & Francis, 2011.

"Cleaning and Contamination Control in Medical Devices" by Barbara Kanegsberg and Edward Kanegsberg, in "Cleaning and Cleaning Validation Volume 2" Paul Pluta ed., PDA DHI Technical Book, 2013.

Validated Cleaning Technologies for Pharmaceutical Manufacturing by Destin A. LeBlanc (Feb 28, 2000).

Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing by Destin A. LeBlanc (2006).