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Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation[1]

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1. Scope

1.1 This guide applies the life-cycle approach to cleaning process validation, which includes the development, qualification, and verification of cleaning processes. It is applicable to pharmaceuticals (including active pharmaceutical ingredients (APIs); dosage forms; and over-the-counter, veterinary, biologics, and clinical supplies) and is also applicable to other health, cosmetics, and consumer products.

1.2 This guide is focused only on the cleaning of equipment product contact surfaces and does not cover disinfection or non-product contact surfaces (which are covered under ~~another~~other existing ~~guide~~ guides: Ref (~~1~~)~~),~~[2]~~.~~ USP <1072>, Guide E2614, and ISO 14698).

1.3 The values stated in SI units are to be regarded as standard. No other units of measurement are included in this standard.

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

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

2. Referenced Documents

2.1 *ASTM Standards:*[3]
E1325 Terminology Relating to Design of Experiments
E2476 Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture
E2614 Guide for Evaluation of Cleanroom Disinfectants
2.2 *ICH Standards:*[4]
Q8 Pharmaceutical Development
Q9 Quality Risk Management
Q10 Pharmaceutical Quality System
Q11 Development and Manufacture of Drug Substances
2.3 *ISO Standards:*[5]
ISO 9000 Quality Management Systems—Fundamentals and Vocabulary
ISO 14698 Guide for Evaluation of Cleanroom Disinfectants, Parts 1–3.
2.4 *Federal Standards:*[6]
21 CFR 211.67 Equipment Cleaning and Maintenance

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[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.03 on General Pharmaceutical Standards.

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[2] The boldface numbers in parentheses refer to a list of references at the end of this standard.

[3] 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.

[4] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, 9, chemin des Mines, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

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

[6] Available from U.S. Government Printing Office, Superintendent of Documents, 732 N. Capitol St., NW, Washington, DC 20401-0001, http://www.access.gpo.gov.

2.5 *USP Standards:*[7]
USP <1072> Disinfectants and Antiseptics

3. Terminology

3.1 *Definitions:*

3.1.1 *acceptable daily exposure, ADE, n*—represents a dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime.

3.1.1.1 *Discussion*—

This is the term used in the *ISPE Risk-MaPP Guide*(**1**) and is equivalent to the acceptable daily intake (ADI) but is associated with any route of administration.

3.1.2 *acceptable daily intake, ADI, n*—measure of the amount of a specific substance (originally applied for a food additive, later also for a residue of a veterinary drug or pesticide) in food or drinking water that can be ingested (orally) on a daily basis over a lifetime without an appreciable health risk. **Ref (2)**

3.1.2.1 *Discussion*—

This term is more commonly associated with food and the oral route of administration.

3.1.3 *cleaning agent, n*—a chemical or mixture of chemicals for the removal of residual material (for example, drug substance, drug product, machining oil, etc.) from equipment surfaces or other critical objects (such as a medical device).

3.1.4 *clean-in-place, CIP, n*—method of cleaning without dismantling equipment.

3.1.5 *cleanability, n*—relative difficulty for cleaning a piece of equipment or product.

3.1.6 *cleaning control strategy, n*—planned set of controls derived from the risk assessment and current cleaning process understanding that ensures reliable and consistent cleaning process performance. **ICH Q10**

3.1.6.1 *Discussion*—

The controls can include parameters and attributes related to materials and tools used for cleaning, cleaning procedure(s), equipment operating conditions, and the associated sampling plans, methods for validation, and routine monitoring.

3.1.7 *cleaning design space, n*—multidimensional combination and interaction of cleaning input variables (for example, product cleanability, equipment design, and so forth) and cleaning process parameters (for example, solvent/cleaning agent concentration, temperature, time, and so forth) that have been demonstrated to provide assurance of achieving acceptable cleaning outputs (for example, active pharmaceutical ingredients (API) residues, cleaning agent residues). **ICH Q8**

3.1.8 *cleaning input variables (parameters), n*—those factors or settings whose values constitute the cleaning process and affect the cleaning output variables.

3.1.8.1 *Discussion*—

These independent variables include product cleanability, equipment size/groups, process residue load, holding times, cleaning agent concentration, cleaning agent type, rinse volume, pH, time, temperature, velocity, pressure, surface coverage, location and cleaning cycle, and so forth.

3.1.9 *cleaning output attributes, n*—these attributes include product and cleaning agent residues remaining on the equipment surfaces after cleaning.

3.1.9.1 *Discussion*—

Bioburden/endotoxin levels and operational considerations such as total cleaning time, holding times and costs may also be cleaning output attributes.

3.1.10 *cleaning process, n*—any process designed to remove process residues from product contact surfaces of manufacturing equipment to levels that ensure patient safety and product quality.

3.1.11 *cleaning process parameters, n*—cleaning agent concentration, temperature, time, and so forth.

[7] Available from U.S. Pharmacopeial Convention (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

3.1.12 *cleaning validation, n*—collection and evaluation of data, from the cleaning process design stage through cleaning at commercial scale, which establishes scientific evidence that a cleaning process is capable of consistently delivering clean equipment. **Ref (3)**

3.1.13 *cleaning verification, n*—confirmation, through the provision of objective evidence, that specified cleaning requirements have been fulfilled. **ISO 90000**

3.1.14 *clean-out-of-place (COP) system, n*—automated system usually used to clean large pieces of equipment or parts of equipment that are disassembled, but too large to clean manually.

3.1.14.1 *Discussion—*

COP systems can range from elaborate washing cabinets with automatic control systems to simple dishwasher type units.

3.1.15 *coupon, n*—representative surface that is typically a rectangular piece of a material of construction in which a known amount of a compound is deposited to simulate a process residue.

3.1.16 *design space, n*—multidimensional combination and interaction of input variables (for example, material attributes) and process parameters that have been demonstrated to provide assurance of quality. **ICH Q8**

3.1.17 *exposure, n*—process by which a human or animal can come into contact with a hazard.

3.1.17.1 *Discussion—*

Exposure may occur through any route (oral, inhalational, dermal, and so forth). Exposure may be short-term (acute exposure), of intermediate duration, or long-term (chronic exposure).

3.1.18 *grouping strategy, n*—strategy of using groups of products or equipment to simplify cleaning validation.

3.1.18.1 *Discussion—*

Products or equipment or both are placed into groups and one or more representatives from the group are chosen for cleaning process performance studies. A grouping strategy shall be scientifically justified.

3.1.19 *manual cleaning, v*—cleaning of equipment, either in place or out of place, by hand and with the aid of brushes, cloths, detergents, and so forth.

3.1.20 *margin of safety, n*—difference between the cleaning acceptance limit (based on ADE) and the process residue data.

3.1.20.1 *Discussion—*

This value can be used as a measure of the overall risk to patient safety presented by the cleaning process. The margin of safety can be measured a number of ways including the process capability index (Cpk) and the process performance index (Ppk).

3.1.21 *maximum allowable carryover, MAC or MACO, n*—maximum amount of carryover from one product to the next.

3.1.21.1 *Discussion—*

The MAC is calculated as a fraction of the lowest therapeutic dose (usually 1/1000) or as a fraction of a lethal dose (LD50) (usually 1/100 000 or 1/1 000 000).

3.1.22 *maximum safe carryover, MSC, n*—maximum amount of carryover of a residual process residue (API, cleaning agent, degradant, and so forth) into the next product manufactured without presenting an appreciable health risk to patients.

3.1.22.1 *Discussion—*

The MSC is calculated from the ADE and the total number of doses in a subsequent batch.

3.1.23 *permitted daily exposure, PDE, n*—represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

3.1.23.1 *Discussion—*

This is the term used by the European Medicines Agency (EMA) and is equivalent to both the ADE and ADI.

3.1.24 *probability, n*—likelihood of occurrence of harm.

3.1.25 *cleaning process residue, n*—any residue, including, but not limited to, APIs, cleaning agents, degradation products, intermediates, excipients, and microbes remaining after a cleaning process.

3.1.26 *qualified statistician, n*—individual with a working knowledge and education, training, or background in statistics who can apply statistical analysis to data from cleaning and cleaning validation studies.

3.1.27 *qualified toxicologist/pharmacologist, n*—individual with specific education and training in toxicology/pharmacology that can apply the principles of toxicology to deriving an ADE or PDE value for required process residues.

3.1.28 *quality by design, n*—systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management. **ICH Q8**

3.1.29 *representative surface, n*—surrogate surface that may be actual processing equipment or has characteristics similar to that of processing equipment and is used for spiking studies.

3.1.30 *visual inspection, n*—process of using the human eye, alone or in conjunction with various aids, as the sensing mechanism from which judgments may be made about the condition of the surface to be inspected.

3.1.31 *visual limit of detection, n*—lowest level of a process residue on a surface (in µg/cm^2 or µg/in.^{2}) that is visible to a qualified inspector under defined viewing conditions.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *CIP system, n*—in this standard, CIP systems include the manufacturing equipment itself (mix tanks, transfer piping, and so forth) as well as the equipment used for cleaning (detergent tanks, rinse tanks, pumps, and so forth).

3.2.2 *cleaning failure modes and effects analysis, FMEA, n*—a procedure to identify all possible failures of a cleaning process or procedure, their effects on cleaning, the likelihood of occurrence, procedure that could result in process residue levels that could put a patient at risk, the toxicity of those cleaning process failures, the likelihood of those cleaning process failures leaving significant levels of process residue, and the probability that the failure or process residues will go undetected.

3.2.2.1 *Discussion*—

The cleaning FMEA can also identify ways to minimize the failures, decrease their likelihood, and improve their detectability. Scales have been developed that can be specifically used for cleaning FMEAs and to measure the risk of cleaning failures (**4-8**).

4. Significance and Use

4.1 Application of the approach described within this guide applies risk-based concepts and principles introduced in ICH Q9. As stated in ICH Q9, the level of effort, formality and documentation for cleaning should also be commensurate with the level of risk.

4.2 Application of the approach described within this guide applies many of the science-based, risk-based, and statistical concepts and principles introduced in the FDA's *Guidance for Industry Process Validation: General Principles and Practices* (**3**).

4.3 This guide supports, and is consistent with, elements from ICH Q8, ICH Q9, ICH Q10, and ICH Q11.

4.4 *Key Concepts*—This guide applies the following key concepts: (*1*) quality risk management, (*2*) science-based approach, (*3*) statistics-based approach, (*4*) process understanding, and (*5*) continued improvement as described in the ICH Q series.

5. Science-Based, Risk-Based, and Statistics-Based Cleaning Process Development and Validation

5.1 Science-based approaches should be applied throughout the cleaning process development and validation process.

5.2 Quality risk management should be applied throughout the cleaning process development and validation process.

5.3 Appropriate statistical analysis should be applied throughout the cleaning process development and validation process.

6. Risk Assessment

6.1 Under ICH Q9, risk assessment is broken into three stages: risk identification, risk analysis, and risk evaluation.

6.2 Risk can be defined as: risk = *f* (probability of occurrence of harm and the severity of that harm).

6.3 For the purposes of cleaning, risk can be further defined as a function of the severity of the hazards of process residues, likelihood and level of process residues, and detectability of process residues.

6.4 For a reliable assessment of risk, scientific means (for example, risk management tools) should be used to identify the hazard presented by a process residue (for example, API, degradation products, intermediates, cleaning agent, bioburden/endotoxin, and so forth), the ability of a cleaning process to remove process residues to levels that are acceptable, and the ability to detect and quantify the presence of process residues after cleaning.

6.5 *Risk Identification*—Risk identification should encompass the identification of process residue hazards, equipment design hazards, and procedural hazards.

6.5.1 *Process Residue Hazard Identification:*

6.5.1.1 The hazard presented by a potential process residue may be determined from a toxicological review performed by a qualified toxicologist or qualified pharmacologist. For an API, this involves a thorough review of all relevant toxicological data available for the process residue under study (**49**). When preclinical and clinical data on APIs are available to review, an ADE can be determined and used as a measure of the severity of hazard presented by a compound. For further information, see the ISPE Risk-MaPP Guide(**1**) or the EMA *Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities*(**49**).

6.5.1.2 When an ADE is not available, such as for intermediates, degradation products, or compounds in early development, alternative approaches such as the threshold of toxicological concern (TTC) may be justified (**49, 510**). Although compounds in early development may not have sufficient safety data to perform a complete analysis, useful information can be found in the chemical structure of a compound to help determine a provisional ADE for the compound. "In silico" (computer-assisted) toxicological assessment or a structure activity relationship can be used to determine provisional ADEs for a compound (**611, ~~7~~12**). For example, a compound in the same structural series of a known API from a given therapeutic class can be treated in the same way as that API, for example, a compound with a propylamine structure would be expected to share properties of this class of antihistamines (**813**). Where data are available on comparative potency, these can be used to adjust the estimated ADE.

6.5.1.3 The hazard of possible bioburden from a previous product and the possibility of microbial proliferation after a cleaning process and the hazards this ~~presents~~ presents, including the need for subsequent disinfection, should also be considered. For example, the hazard(s) presented by holding equipment either in a dirty state or in clean state should be considered or the possibility of endotoxin and the need for subsequent depyrogenation should be considered.

6.5.2 *Equipment Hazard Identification*—The potential hazards presented by equipment design should also be considered, such as the possibility of product buildup. Equipment should be designed to facilitate cleaning, inspection, and monitoring.

6.5.3 *Procedural Hazard Identification*—Before use, cleaning procedures should be subjected to risk assessments, for example, cleaning FMEA or other risk management tools, to minimize risk of failure (for example, to ensure that product buildup is avoided),, improve the cleaning procedures, and make the cleaning procedures more reliable and robust.

6.6 *Risk Analysis:*

6.6.1 After identifying the hazards posed, the risks associated with them should be analyzed. This risk analysis should involve the cleaning process development, facility/equipment design review, cleaning procedure review, and the selection of analytical methods. The analysis should also determine what steps can be taken to mitigate the identified risks.

6.6.2 The risk analysis should show how cleaning may affect the patient safety and quality of the next product.

6.6.3 The impact of the different factors (process residue, cleaning/rinsing agents, equipment engineering, and so forth) on the outcome of the cleaning process should be analyzed.

6.6.4 The cleaning process risk analysis can help to determine the necessary cleaning qualifications and identify appropriate risk control mechanisms.

6.6.5 *Process Residue Characterization:*

6.6.5.1 The chemistry of process residues should be understood to design an effective and efficient cleaning cycle, for example, cleanability of process residues (for example, highly insoluble or strongly adhesive residues) and potential interactions (for example, staining, corrosion) of process residues with equipment.

6.6.5.2 The chemistry and potential interactions between process residues and chemicals used as part of cleaning processes should also be understood, for example, the solubility of process residues in cleaning agents or rinsing agents should be considered to avoid situations in which process residues are not removed or whether degradation products may be formed that may be harder to clean or more toxic than the original process residue.

6.6.6 *Equipment Design for Cleanability:*

6.6.6.1 The design of equipment has an impact on its cleanability. Equipment design should be considered as part of the risk analysis taking into consideration the likely type of cleaning process that will be applied to that equipment. The variables and attributes related to equipment design should be identified and linked to the cleaning critical attributes using the appropriate risk assessment tool(s). Examples of equipment design considerations may include: materials of construction, presence of dead legs or other areas in which material could become trapped, or drainability.

6.6.6.2 Where satisfactory cleaning results cannot be achieved because of limitations in the equipment design, the equipment may need to be modified, dedicated, or replaced.

6.6.7 *Evaluation of Historical Cleaning Data*—The history of cleanings (along with any deviations, investigations, and corrective actions) should be reviewed. This cleaning process understanding and knowledge can provide useful information in a risk analysis and may help identify cleaning process parameters to be used in cleaning process development studies and determine the likelihood of a cleaning failure (ICH Q10).

6.6.8 *Levels of Cleaning*—Manufacturing equipment may require different levels of cleaning and validation under different circumstances. To determine the appropriate cleaning level, the type of product manufactured on the equipment (for example,

intermediates, APIs, finished products) should be considered and the risks to patient safety and product quality should be understood. A cleaning process can then be developed to achieve the necessary results. There may be several levels of cleaning based on the level of risk, for example:

6.6.8.1 Cleaning between different products,

6.6.8.2 Cleaning between similar products,

6.6.8.3 Cleaning during campaigning (cleaning between batches of the same product),

6.6.8.4 Cleaning of dedicated equipment,

6.6.8.5 Cleaning after equipment maintenance,

6.6.8.6 Cleaning after elapse of permissible storage/hold time of clean equipment,

6.6.8.7 Cleaning after sampling, and

6.6.8.8 Cleaning after non-routine operations.

6.6.9 *Cleaning Process Development*—Cleaning processes should not be adopted randomly or chosen based on past use. Cleaning processes should be developed to reduce process residues levels as low as practical and determine the appropriate cleaning agents for this purpose. Cleaning processes that have been optimized through the selection of the most appropriate cleaning agents and cleaning parameters can offer the greatest ability to reduce process residues in the shortest time to the lowest level of risk. The output of the cleaning process development should be used to create the cleaning standard operating procedure (SOP).

6.6.9.1 *Bench-Scale Studies:*

(1) Laboratory scale or "bench-scale" studies can provide valuable sources of cleaning process knowledge and cleaning process understanding (**914**). The studies may be conducted by spiking the process residue(s) on coupons and then subjecting the coupons (after drying) to varying cleaning conditions. The studies could also be conducted in small-scale equipment designed to simulate the actual manufacturing equipment.

(2) Bench-scale studies can be quick, economical, and provide information on how difficult a product is to clean, which cleaning agent provides optimal cleaning, which cleaning input variables are critical, and whether dirty hold time studies may be necessary. Cleaning process knowledge and cleaning process understanding gained from bench scale studies may be directly applicable to full-scale cleaning processes but differences between full scale and bench scale should be considered.

6.6.9.2 *Cleaning Parameter Determination*—The effects and the interactions of input variables affecting cleaning should be evaluated. The variables typically associated with cleaning are: time, temperature, cleaning agent chemistry, mechanical action, product cleanability, and amount of process residue.

6.6.9.3 *Design of Experiments (DoE) and "Cleaning Design Space:"*

(1) To improve or optimize cleaning processes, experiments can be designed to examine the effects of cleaning input parameters on cleaning output variables. These inputs can be assigned as factors in a DoE (Terminology E1325) and the effects and interactions of varying these factors on the outputs can be measured as responses.

(2) Typical cleaning input parameters include product cleanability, equipment size/groups, process residue concentration, holding times, cleaning agent type and concentration, wash/rinse temperature/time/volume, flow, pressure, and spray ball type/location.

(3) The typical cleaning output variables are the product and cleaning agent residues. Bioburden levels and operational considerations such as cleaning times, holding times, and costs may also be considered.

(4) DoE are used for determining a "cleaning design space"[8] that provides many benefits including justification of product or equipment grouping and process change control strategies. If changes to the cleaning process or equipment are considered, the results of a risk review can provide information regarding the impact on cleaning design space and the need for additional studies or testing.

(5) "Cleaning design space" also provides important input into the cleaning control strategy.

6.6.9.4 *Cleaning Agent Selection:*

(1) Cleaning agents should be selected based on scientific principles and the level of hazard they pose. This selection should also be based on cleaning process development studies (for example, bench-scale studies), compatibility with the materials of construction of the equipment, and should not be based simply on availability or only for harmonization purposes.

(2) The composition of a cleaning agent and its variability should be known. The ability to detect residues of the cleaning agent should also be considered.

6.6.10 *Cleaning Equipment Design and Qualification:*

6.6.10.1 Equipment used to support cleaning should be designed with the same attention to detail as directed to manufacturing equipment. Equipment design specifications should be capable of meeting the required cleaning specifications from bench scale and cleanability studies. This equipment should be suitably located to facilitate proper cleaning during operations.

6.6.10.2 A documented risk assessment should determine the level of risk presented by the cleaning equipment and the controls that should be established to mitigate risks.

[8] Note that under ICH Q8 Design Space is submitted in the filing but this is not the case for cleaning.