Designation: E3106 – 22

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

This standard is issued under the fixed designation E3106; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide 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)); all dosage forms; over-the-counter medicinal and neutraceutical products, veterinary products, biologics, clinical supplies, advanced therapy medicinal products (ATPM), medical device manufacturing; 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 medical device surfaces and does not cover disinfection, sterilization, or non-product contact surfaces (which are covered under other existing guides: Ref (**1**),[2] USP <1072>, Guide E2614, ISO 14698, and ISO 14937).

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
E2281 Practice for Process Capability and Performance Measurement
E2476 Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture
E2500 Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment
E2614 Guide for Evaluation of Cleanroom Disinfectants
E3219 Guide for Derivation of Health-Based Exposure Limits (HBELs)
E3263 Practice for Qualification of Visual Inspection of Pharmaceutical Manufacturing Equipment and Medical Devices for Residues
F3127 Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices
F3357 Guide for Designing Reusable Medical Devices for Cleanability
G121 Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents
G122 Test Method for Evaluating the Effectiveness of Cleaning Agents and Processes

2.2 *ICH Guidelines:*[4]

Q8 Pharmaceutical Development
Q9 Quality Risk Management
Q10 Pharmaceutical Quality System
Q11 Development and Manufacture of Drug Substances

[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.

Current edition approved Nov. 1, 2022. Published December 2022. Originally approved in 2017. Last previous edition approved in 2018 as E3106 – 18ε1. DOI: 10.1520/E3106-22.

[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.

Q12 Implementation Considerations for FDA-Regulated Products

2.3 *ISO Standards:*[5]

ISO 9000 Quality Management Systems—Fundamentals and Vocabulary

ISO 10993-1 Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process

ISO 14698 Guide for Evaluation of Cleanroom Disinfectants, Parts 1–3.

ISO 14937 Sterilization of Health Care Products—General Requirements for Characterization of a Sterilizing Agent and the Development, Validation and Routine Control of a Sterilization Process for Medical Devices

ISO 17664 Processing of health care products

2.4 *Federal Regulations:*[6]

21 CFR 211.67 Current Good Manufacturing Practice for Finished Pharmaceuticals—Equipment Cleaning and Maintenance

2.5 *European Regulation:*[7]

European Commission Directorate for Health and Food Safety EudraLex Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Annex 15: Qualification and Validation

2.6 *USP Standards:*[8]

USP <1072> Disinfectants and Antiseptics

3. Terminology

3.1 *Definitions:*

3.1.1 *acceptable daily exposure, ADE, n*—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 permitted daily exposure (PDE). The ADE is associated with any route of administration. Toxicity scales can be used to evaluate severity of the hazard posed by product being cleaned.

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

3.1.3 *clean-in-place, CIP, n*—manual, semi-automated, or automated methods of cleaning equipment in situ without dismantling equipment.

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

3.1.4.1 *Discussion*—COP systems can range from elaborate washing cabinets with automatic control systems to simple dishwasher type units. Many medical devices may be cleaned in these types of systems (for example, mechanical washers, ultrasonic baths, and so forth).

3.1.5 *cleanability, n*—relative difficulty for cleaning a piece of equipment, product, or device. **G122, F3357**

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 effectiveness factor, CEF, n*—fraction of contaminant removed, or remaining, from an initially contaminated test coupon and determined by gravimetric or other analytical techniques (for example, total organic carbon analysis, and so forth). **G122**

3.1.8.1 *Discussion*—The CEF is a laboratory bench-scale measurement of the relative difficulty of a compound/product to be cleaned that can be compared to other compounds/products using standardized conditions for temperature, agitation, type of cleaning agent, and cleaning agent concentration. The tests can be performed using Manual Cleaning Models, Clean-Out-of-Place (COP) Models, or Clean-in-Place (CIP) Models.

3.1.8.2 *Discussion*—The method can also be customized to use existing parameter settings of a cleaning process as specified by a company.

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

3.1.9.1 *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.

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

3.1.10.1 *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).

[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.

[7] Available from the European Commission, https://ec.europa.eu/health/documents/eudralex/vol-4_en.

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

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

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

3.1.12 *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.

3.1.13 *cleaning process capability, n*—statistical analysis that is used to find out how well a given cleaning process meets a set of specification limits, including a measure of how well a process performs. **E2281**

3.1.13.1 *Discussion*—Process capability scales are used to measure the probability of an occurrence and are a component of risk posed by cleaning processes. **(2)**

3.1.14 *cleaning process parameters, n*—temperature, time, cleaning agent concentration, and others as identified.

3.1.15 *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)**

3.1.16 *cleaning verification, n*—confirmation, through the provision of objective evidence, that specified cleaning requirements have been fulfilled. **ISO 9000**

3.1.17 *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.

3.1.18 *critical quality attributes, n*—physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. **ICH Q8**

3.1.19 *design of experiments, DoE, n*—experimental approach to determine what factors (that is, cleaning process parameters) have a main effect on the output (critical quality attributes) of a process and which factors interact with other factors and affect the output.

3.1.19.1 *Discussion*—A large number of cleaning process parameters can be studied in a relatively small experiment using definitive screening designs that prevent the confounding of main effects with interactions and can also detect nonlinearity.

3.1.20 *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**

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

3.1.21.1 *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).

3.1.22 *grouping strategy, n*—approach of using groups of products or equipment that share materials of construction and share a common cleaning procedure as representative of the group to simplify cleaning validation.

3.1.22.1 *Discussion*—Products or equipment (or both) or families of products (medical devices ISO 17664-1, Section 4.3) 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.

3.1.23 *hardest to clean equipment or device, n*—equipment or device that has been shown empirically to be the most difficult to remove process residues from.

3.1.23.1 *Discussion*—This is a piece of equipment or device that is used as representative of other equipment or devices in a group to simplify cleaning validation studies.

3.1.24 *hardest to clean product, n*—product (or API) that has been shown empirically to be the most difficult to remove from manufacturing or medical device surfaces.

3.1.24.1 *Discussion*—This is determined by laboratory analysis following Practice G121 and Test Method G122 and comparing the CEF results among the compounds to determine which has the highest CEF (remaining).

3.1.25 *health-based exposure limit, HBEL, n*—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.

3.1.25.1 *Discussion*—The procedure for calculating an HBEL proposed by the EMA in their guideline is the same method for establishing the Permitted Daily Exposure (PDE) as described in Appendix 3 of ICH Q3C (R4) and Appendix 3 of VICH GL 18.

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

3.1.26.1 *Discussion*—Medical devices manually cleaned can involve both process and devices to the extent of the defined validated cleaning process.

3.1.27 *maximum daily dose, MDD, n*—highest dose that a patient may be administered in one day (24 h); for example, for a 100 mg tablet that can be administered up to four times in a day, the MDD is 400 mg.

3.1.27.1 *Discussion*—MDDs can often be found on the package insert of the drug product.

3.1.28 *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.

3.1.28.1 *Discussion*—The MSC is calculated from the HBEL and the total number of doses in a subsequent batch. It is total mass amount of material (µg or mg) that can be safely carried over into the next batch of product. The total number of doses in a batch is determined by dividing the maximum daily dose (MDD) of the next product into the batch size of the next product.