



Designation: E3106 – 22

Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation¹

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 – 18^{ε1}. 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>.