



Designation: E3418 – 23

Standard Practice for Calculating Scientifically Justifiable Limits of Residues for Cleaning of Pharmaceutical and Medical Device Manufacturing Equipment and for Medical Devices¹

This standard is issued under the fixed designation E3418; 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 practice provides procedures for calculating safe and scientifically justifiable limits of residues for use in cleaning validation studies of pharmaceutical/biopharmaceutical/medical device manufacturing equipment surfaces and medical device surfaces.

1.2 The procedures in this standard practice for calculating safe limits of chemical residues are based on Guide E3219.

1.3 This practice applies to pharmaceuticals (including active pharmaceutical ingredients (APIs); dosage forms; and over-the-counter, veterinary, biologics, and clinical supplies) and medical devices following all manufacturing and cleaning. This practice is also applicable to other health, cosmetics, and consumer products.

1.4 This practice applies to all types of chemical residues (including APIs; intermediates, cleaning agents, processing aids, machining oils, etc.) that could remain on manufacturing equipment surfaces or on medical devices that have undergone all manufacturing steps including cleaning. This practice does not cover extractables and leachables (see ISO 10993-17).

1.5 This practice applies to microbiological residues that may be present on manufacturing equipment surfaces or on medical devices that have undergone all manufacturing steps including cleaning and does not cover disinfection or sterilization.

1.6 *Exclusions*—Medical devices that do not make patient contact; non-product contact surfaces (which are discussed in other existing guides: Ref (1)², PDA TR 29, USP <1072>, Guide E2614, ISO 14698, and ISO 14937).

¹ This practice is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.13 on Process Evaluation and Control.

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

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

1.8 *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.*

1.9 *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

E2476 Guide for Risk Assessment and Risk Control as it Impacts the Design, Development, and Operation of PAT Processes for Pharmaceutical Manufacture

E2586 Practice for Calculating and Using Basic Statistics

E2587 Practice for Use of Control Charts in Statistical Process Control

E2614 Guide for Evaluation of Cleanroom Disinfectants

F2847 Practice for Reporting and Assessment of Residues on Single-Use Implants and Single-Use Sterile Instruments

E3106 Guide for Science-Based and Risk-Based Cleaning Process Development and Validation

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

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.

F3127 Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices

2.2 ICH Guidelines:⁴

ICH Q9 Quality Risk Management

2.3 ISO Standards:⁵

ISO 10993-1 Biological Evaluation Of Medical Devices—Part 1: Evaluation and testing within a risk management process

ISO 10993-12 Biological Evaluation Of Medical Devices—Part 12: Sample Preparation And Reference Materials

ISO 10993-17 Biological Evaluation of Medical devices—Part 17: Establishment of allowable limits for leachable substances

ISO 13485 Medical Devices – Quality management systems – Requirements for regulatory purposes

ISO 14644-2 Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration

ISO 14698 Cleanrooms and associated controlled environments

ISO 14937 Biocontamination control—Part 1: General principles and methods

ISO 19227 Implants for Surgery—Cleanliness of orthopedic implants

ISO 21726 Biological Evaluation of Medical devices—Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents

2.4 Federal Regulations:⁶

21 CFR 211.67 Equipment Cleaning and Maintenance

21 CFR 820 Quality System Regulation

2.5 United States Pharmacopoeia:⁷

USP <61> Microbiological Examination Of Nonsterile—Products: Microbial Enumeration Tests

USP <62> Microbiological Examination Of Nonsterile Products: Tests For Specified Microorganisms

USP <85> Bacterial Endotoxins

USP <161> Transfusion and Infusion Assemblies and Similar Medical Devices

USP <771> Ophthalmic Products—Quality Tests

USP <1072> Disinfectants and Antiseptics

USP <1085> Guidelines on Endotoxins Test

USP <1111> Microbiological Examination Of Nonsterile Products: Acceptance Criteria For Pharmaceutical Preparations And Substances For Pharmaceutical Use

2.6 Other Standards:

PDA TR 29 Points to Consider for Cleaning Validation⁸

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 International Society of Pharmaceutical Engineers (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 *action limit, n*—an established value that, when exceeded, indicates a process is outside of its normal operating conditions.

3.1.2.1 *Discussion*—A response to such an excursion requires a documented investigation, product impact assessment, and corrective actions based on the results of that investigation (PDA TR 29). Action level of a parameter set by the user which, when exceeded, requires immediate intervention, including investigation of cause, and corrective action (ISO 14644-2). An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation (2).

3.1.3 *alert limit, n*—an established value that, when exceeded, provides an early warning of a potential drift from the normal operating conditions and validated state.

3.1.3.1 *Discussion*—This type of warning does require an appropriate documented investigation (for example, trend analysis) and may require corrective actions depending on the results of the investigation (PDA TR 29). The alert limit is the level of a parameter set by the user giving early warning of a drift from normal conditions, which, when exceeded, should result in increased attention or corrective action (ISO 14644-2). An established microbial or airborne particle level giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follow-up to address the potential problem. Alert limits are always lower than action limits (2).

3.1.4 *analyte, n*—a substance (usually a residue) for which an analysis is being performed.

3.1.4.1 *Discussion*—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.

3.1.5 *cleaning limit, n*—highest level of residue that is acceptable for exposure to the patient or on the medical device.

3.1.5.1 *Discussion*—Cleaning limits are used to evaluate cleaning process performance for pharmaceutical manufacturing equipment or medical device surfaces.

3.1.6 *cleaning performance limit, n*—performance-based limit derived from the cleaning process data.

⁴ Available from International Council 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 International Organization for Standardization (ISO), ISO Central Secretariat, Chemin de Blandonnet 8, CP 401, 1214 Vernier, Geneva, Switzerland, <https://www.iso.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 U.S. Pharmacopeial Convention (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, <http://www.usp.org>.

⁸ Available from Parenteral Drug Association (PDA), 4350 East West Highway, Suite 600, Bethesda, MD 20814, www.pda.org.