Designation: E3418 – 23

Standard Practice for Calculating Scientifically Justifiable Limits of Residues for Cleaning of Pharmaceutical and Medical Device Manufacturing Equipment and for Medical Devices[1]

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).

1.7 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

[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.

Current edition approved Nov. 1, 2023. Published November 2023. DOI: 10.1520/E3418-23.

[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.

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 Validation[8]

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.

3.1.6.1 *Discussion*—The HBEL-based limit can be used as an action limit when this limit is low with appropriate scientific justification based on the level of risk. With low risk products the HBEL may be too high and alternative limits should be identified (see Guide E3106).

3.1.7 *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 (see Guide E3106).

3.1.7.1 *Discussion*—Residues may be physical, chemical, bioburden, endotoxin, and even visual. For medical devices, a residue is 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. A residue may or may not pose a risk to patients.

3.1.8 *cleaning qualification, n*—a cleaning qualification confirms the cleaning process design and demonstrates that the commercial cleaning process performs as expected (see Guide E3106).

3.1.9 *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 (see Guide E3106).

3.1.10 *cleaning verification, n*—confirmation, through the provision of objective evidence, that specified cleaning requirements have been fulfilled (see Guide E3106).

3.1.11 *contaminant, n*—any material that potentially adversely impacts the assembly, the functioning of the device, and/or shows undesirable interaction with the host.

3.1.11.1 *Discussion*—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 (see Guide F3127).

3.1.12 *control limits, n*—limits on a control chart that are used as criteria for signaling the need for action or judging whether a set of data does or does not indicate a state of statistical control based on a prescribed degree of risk (see Practice E2587).

3.1.12.1 *Discussion*—Control limits can be used as "alert" or "action" limits. Alert limits can be set at two standard deviations and action limits can be set at three standard deviations.

3.1.13 *decision interval, H, n*—the distance between the center line and the control limits (see Practice E2587).

3.1.14 *decision interval multiplier, h, n*—multiplier of standard deviation that defines the decision interval, H (see Practice E2587).

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

3.1.15.1 *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).

3.1.16 *health based exposure limit, HBEL, 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 (see Guide E3219).

3.1.16.1 *Discussion*—This is the term used in the European Medicines Association (EMA) Guideline on health based exposure limits **(3)** and is equivalent to the acceptable daily exposure (ADE) and the permitted daily exposure (PDE).

3.1.17 *maximum safe carryover, MSC, n*—maximum amount of carryover of a residual cleaning process residue (API, cleaning agent, degradant, and so forth) into the next product manufactured without presenting an appreciable health risk to patients (see Guide E3106).

3.1.17.1 *Discussion*—The MSC is calculated from the HBEL (ADE/PDE) and the total number of doses in a subsequent batch.

3.1.18 *maximum safe surface residue MSSR, n*—maximum amount of residual residue cleaning process residue (API, cleaning agent, degradant, and so forth) that may remain on manufacturing equipment or medical device surfaces without presenting an appreciable health risk to patients (see Guide E3106).

3.1.18.1 *Discussion*—The MSSR is calculated from the MSC and the total shared product contact surface area of the equipment or total surface area of the device that may result in patient exposure and is expressed in $\mu g/cm^2$, $mg/in.^2$, and so forth. The MSSR is widely used in cleaning validation programs, such as cleaning process development studies, cleaning verification or qualification studies, analytical method validation recovery studies, as well as for qualification of visual inspection.

3.1.19 *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.

3.1.19.1 *Discussion*—This is the term used in ICH Q3C and by the European Medicines Agency (EMA) and is equivalent to both the ADE and ADI **(4)**.

3.1.20 *qualified expert, n*—individual with specific education and training in toxicology/pharmacology/pharmacotherapy and risk assessment methods that can apply the principles of toxicology to deriving an HBEL (see Guide E3219).

3.1.20.1 *Discussion*—The European Medicines Agency states that health based exposure limits should be determined by a person who has adequate expertise and experience in toxicology/pharmacology, familiarity with pharmaceuticals as well as experience in the determination of health-based exposure limits such as occupational exposure levels (OEL) or permitted daily exposure (PDE) **(3)**.

3.1.21 *recovery study, n*—laboratory study combining the sampling method and analytical method to determine the quantitative recovery of a specific residue for a defined surface (see Guide F3127). Laboratory study evaluating a sampling method (for example, swab, rinse, visual examination, and so

forth) in combination with an analytical method (for example, TOC, HPLC, visual inspection, and so forth) to determine the quantitative recovery of a specific residue (see Guide E3106).

3.1.21.1 *Discussion*—Recovery studies are performed by spiking specific residues onto a defined surrogate surface (coupon) or onto surfaces of actual processing equipment or onto actual medical devices and sampling these surfaces. Adequate recovery should be defined and demonstrated to justify the appropriateness of the method (see Practice F2847). Recovery should be shown to be possible from **all** product contact materials sampled in the equipment with **all** the sampling methods used (**5**). If a reduction in the number of product contact materials on which recovery studies should be performed is desired this may be possible if justified through a risk assessment (for example, consider patient exposure from product contact surface).

3.1.22 *surrogate surface, n*—part that is used as a substitute for a piece of manufacturing equipment or a medical device surface (see Guide E3106).

3.1.22.1 *Discussion*—For pharmaceuticals, surrogate surfaces are typically "coupons" which are typically a rectangular piece of a material of construction on which a known amount of a compound is deposited to simulate a cleaning process residue. For medical devices, surrogate surfaces may be in the form of "coupons" but are often parts of a medical device, or the entire medical device itself.

3.1.23 *visual residue limit (VRL), n*—lowest level of a cleaning process residue on a surface (in µg/cm^2 or µg/in.^{2}) that is visible to a qualified inspector under defined viewing conditions (see Practice E3263).

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *maximum daily dose, MDD, n*—the highest dose that a patient may be administered in one day (that is, 24 hours) and is a daily dose limitation on certain drugs imposed by the regulatory agencies for safety reasons.

3.2.1.1 *Discussion*—The MDD is determined from the Dosage and Administration (D&A) section of the reference listed drug (RLD) or reference standard (RS) labeling.

3.2.2 *maximum number of applications, MNA, n*—the maximum number of applications per day or the maximum number of times a product can be administered per day.

3.2.3 *maximum number of units, MNDU, n*—maximum number of units administered/day.

3.2.4 *maximum quantity, MQ, n*—maximum quantity administered in each dose/application.

3.2.4.1 *Discussion*—This could be in the form of the weight of a single unit (mg/unit); the maximum volume administered in a single dose (in mL/dose); the volume of a drop (mL/drop); the amount applied in each application (g/application or mL/application).

3.2.5 *medical device, n*—an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes (**6**).

3.2.5.1 *Discussion*—Instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more specific medical purpose and does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means (ISO 13485).

3.2.5.1 *Discussion*—ISO 13485 states that the organization shall establish documented requirements for cleanliness of product. Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality (21 CFR 820). These requirements would include the setting of acceptance criteria.

3.2.6 *scientifically justifiable, adj*—able to be shown to be defensible based on solid scientific evidence.

3.2.6.1 *Discussion*—The FDA 1993 Cleaning Validation Guidance Section IV Evaluation of Cleaning Validation (**6**) specifies that "the objective of the inspection is to ensure that the basis for any limits is scientifically justifiable," and "... the test of any validation process is whether scientific data shows that the system consistently does as expected and produces a result that consistently meets predetermined specifications." Therefore, cleaning data should support a conclusion that residues have been reduced to an "acceptable level." This indicates that the data must be assessed for patient risk and evaluated. Within this context, residue limits based on HBELs and residue limits based on statistical process control (SPC) are scientifically justifiable.

3.2.7 *smallest batch size, n*—batch size with the smallest volume or weight manufactured on shared equipment.

3.2.7.1 *Discussion*—The smallest batch size is an important parameter in the calculation of safe limits as the smallest batch would have the highest concentration of residue carryover resulting in highest level of exposure to patients.

4. Significance and Use

4.1 *Pharmaceutical Discussion:*

4.1.1 The origins for the calculation of cleaning validation limits for pharmaceuticals date back to the 1980's with the publication of an article in 1984, that stated that "limits must be safe and acceptable and in line with residual limits set for various substances in foods" (**7**). A second article in 1989 expanded upon these ideas adding that an "effect threshold" should be established in collaboration with toxicology and medical authorities (or alternatively, an appropriate safety factor. For example, 10× or 100× could be superimposed) and

finally that limits for surface residue levels could then be calculated based on a smallest batch size/maximum dose combination. This article further mentioned that this calculation leads to many limits that could be verified through visual inspection (**8**). A third article in 1993, proposed the use of a combination of limits suggesting that carryover of product residues needed to meet these three criteria:

(1) No more than 0.001 dose of any product will appear in the maximum daily dose of another product,

(2) No more than 10 ppm of a product will appear in another product, and

(3) No quantity of residue will be visible on the equipment after cleaning procedures are performed (**9**).

4.1.2 In 1993, United States Food and Drug Administration (USFDA) issued a guide for its inspectors requiring that "the basis for any limits must be scientifically justifiable" (**6**). In 1996, USFDA proposed that, in addition to penicillin, certain "classes" of compounds would also need to be manufactured in dedicated facilities and would expect manufacturers to identify any drugs that present the risk of cross-contamination and to implement measures necessary to eliminate that risk (**10**). Otherwise, nothing short of dedicated facilities or equipment would be sufficient. In 2005, the European Medicines Agency (EMA) similarly announced that it would require dedicated facilities for certain medicines in addition to potent sensitizers (**11**).

4.1.3 In response to these pending regulatory requirements, a guideline was published in 2010 by ISPE which introduced the concept of a health-based limit for calculating cleaning limits known as the Acceptable Daily Exposure (ADE) (**1**). The demonstration of adequate cleaning and control against ADE derived limits could avoid facility or equipment dedication. Several articles were published discussing why the dose-based and median lethal dose (LD_{50}) should no longer be used and should be replaced with the limits based on the ADE (**12-15**).

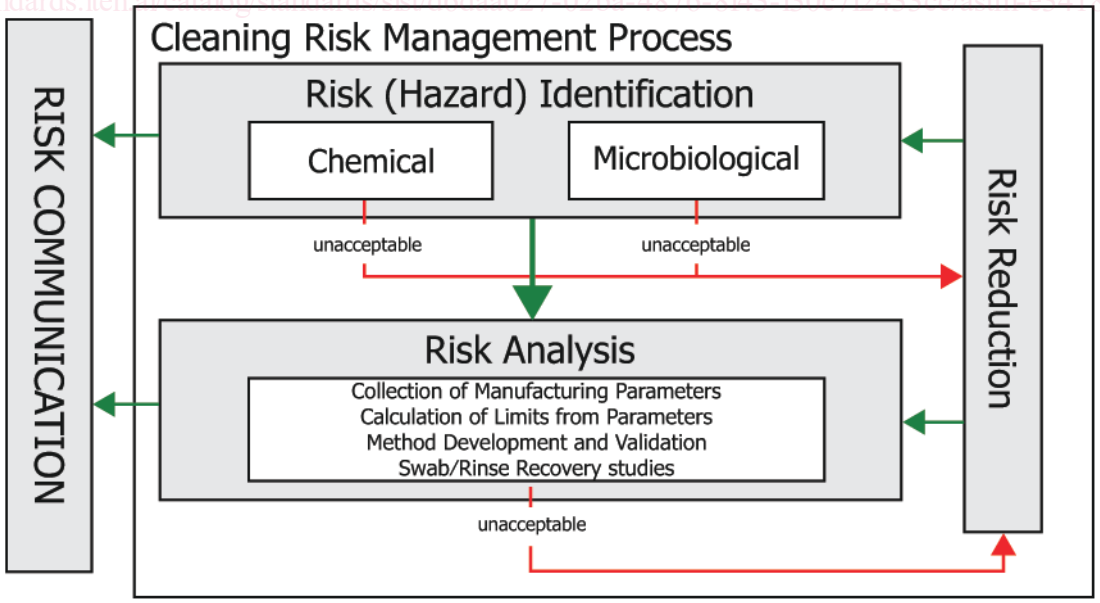
4.1.4 In 2015, EMA issued a guidance requiring the use of health based exposure limits (HBELs) for use in calculating cleaning limits (**2**). This requirement has now been incorporated into the European and Pharmaceutical Inspection Co-operation Scheme Good Manufacturing Practices (**5 and 16**) and has been adopted by Health Canada (**17**) and the World Health Organization (**18**).

4.2 *Medical Device Discussion:*

4.2.1 The medical device industry is very broad and includes many diverse devices that have been handled differently than pharmaceuticals.

4.2.2 For example, cleaning acceptance limits for implantable medical devices have been based historically on testing after the cleaning process is completed by doing biological safety assessments that show that the final packaged product is safe and effective (ISO 19227, ISO 10993-1). Initial cleaning limits might be derived from historical data on the same types of devices using the same manufacturing processes and materials as a starting point and coupling that with clinical history that shows the devices produced using this methodology are safe and effective. Then biological safety testing, including extractables, is performed on devices exposed to the validated, controlled cleaning process.

4.2.3 The extractables testing also shows that the limits that were established for other manufacturing residuals that carry through on the part after cleaning are also at levels low enough to mitigate any local or systemic adverse reaction (this may be toxicological risk assessment of the extractables test data as well as biological testing).



All medicinal products must have HBELs determined (**2**). Other chemical compounds identified as hazards to patients in the risk (hazard) identification step that cannot be eliminated or replaced should have HBELs determined if acceptable safety assessments or risk assessments are not available (see Guide E3219). After HBELs have been determined, manufacturing parameters such as batch sizes, maximum daily doses, total share surface areas, etc. are documented in the risk analysis step and used to calculate safe limits for swab and rinse samples.

FIG. 1 ASTM E3106 Risk (Hazard) Identification and Risk Analysis Steps (modified from FIG. 3 in E3106)

4.2.4 While many medical devices use the approach described above, some medical devices can benefit from using an HBEL approach similar to pharmaceuticals. If an HBEL approach is used with a medical device, a risk assessment (this could be the HBEL monograph (see Guide E3219)) should address other potential risks (for example, patient exposure at the tissue level) from residue levels on the device beyond the general toxicological risk assessments typically performed for pharmaceuticals.

4.2.5 Application of the approach described within this guide applies science-based and risk-based concepts and principles for calculation of cleaning validation safe limits and performance-based limits (for example, statistical process control) introduced in Guide E3106.

NOTE 1—All limit calculations in this standard assume there will be homogeneity of residue levels on equipment and device surfaces achieved after an effective and consistent cleaning as per Guide E3106.

4.2.6 Application of the approach described within this guide applies the science-based and risk-based concepts and principles for derivation of health based exposure limits introduced in Guide E3219.

4.2.7 Application of the approach described within this guide applies the science-based and risk-based concepts and principles for derivation of visual residue limits introduced in Practice E3263.

4.2.8 *Key Concepts*—This guide applies the following key concepts: (*1*) health based exposure limits, (*2*) quality risk management, (*3*) science-based approach, (*4*) statistics-based approach, (*5*) visual residue limits, and (*6*) statistical process control (SPC) limits.

5. Procedure

5.1 Users of this standard should define what equipment should be included in the calculation of limits (for example, single pieces of equipment vs. equipment trains). This decision should be based on a risk assessment of the cleaning process. This standard does not recommend calculating a single limit for all cleaning processes for all equipment and manufacturing trains within a facility.

5.1.1 For pharmaceuticals and those medical device products that use the HBEL, the equations used for calculating safe and scientifically justified swab and rinse sample limits are comprised of three sub-equations:

(1) HBEL,
(2) Maximum safe carryover (MSC), and
(3) Maximum safe surface residue (MSSR).

5.1.2 The following sections will discuss the parameters used in the calculation of these sub-equations, how these parameters should be determined or derived, and how they interact with each other. The first three sub-equations are generally combined into one general equation that calculates down to a safe analytical limit, usually a swab or rinse limit (see 5.6).

5.2 *Calculating Health Based Exposure Limits (Guide E3219)*—The first step in the calculation of safe limits for residues is the determination of the HBEL. HBELs are based on substance-specific properties (toxicity, type of effect, severity of effect, pharmacology, potency, etc.). HBELs should be determined for all compounds identified during the hazard identification of the cleaning risk assessment as shown in Fig. 1 unless they can be excluded by available safety assessments or risk assessments (see Guide E3219 and **(19)**). Guide E3219 provides guidance for setting HBELs from investigational new products to products in commercial distribution. HBELs should be determined by qualified experts following Guide E3219 and in accordance with regulatory guidance and expectations **(19 and 20)**.

5.2.1 *Use of Substitute Limits*—In certain cases, such as with older drugs with limited toxicological/clinical data or investigational new medicines in early phase clinical trials, as well as the raw materials used in many of the machining fluids and other processing aids used to produce a medical device, there may be insufficient data to support the calculation of an HBEL. In these circumstances, scientifically justified limits may be used in place of a calculated HBEL. There are several different approaches for establishing an HBEL that have been used in the past, such as the thresholds of toxicological concern (TTCs). TTCs have been determined through statistical analysis for several types of compounds (see ISO 21726 and Guide E3219 Section 7: Incomplete Datasets with a High Level of Uncertainty).

5.2.1.1 Substitute limits should not be seen as permanent or as a replacement for a scientifically derived HBEL. As information becomes available, appropriate HBELs should then be determined.

5.3 *Calculation of the Maximum Safe Carryover (MSC) of Residue into Next Product Batch*—After the determination of the HBELs, the next step is the calculation of the maximum safe carryover (MSC) of the residue into the batch of the subsequently manufactured product. For chemical residues (such as the drug active or cleaning agent, etc.), this is the maximum amount of residue carryover into the next batch that is considered safe and is typically given in milligrams or grams. MSC is calculated by multiplying the HBEL by the smallest batch size (SBS) of the next product divided by the maximum daily dose (MDD) of the next product. The SBS divided by the MDD provides the total number of daily doses in the batch of the next product. Multiplying the total number of daily doses in the batch of the next product by the HBEL (maximum daily exposure that is safe) gives the maximum amount of residue carryover on the equipment that is considered to be safe.

The MSC is calculated using the following equation:

$$\mathrm{MSC} = \mathrm{HBEL} \times \frac{\mathrm{SBS}}{\mathrm{MDD}} \tag{1}$$

5.3.1 The SBS is determined from the master batch records of the products processed in the equipment under consideration. The SBS should be used for calculating safe limits for each cleaning process under investigation.

5.3.2 *Maximum Daily Dose (MDD)*—The MDD may be determined from several sources. The simplest source is the medication package insert/outsert for the product (for example, 'United States Package Insert' or the 'Summary of Product Characteristics' in the EU) which typically list specific maximum daily dosing. The MDD may be given as "No more than

TABLE 1 Batch Sizes of Various Products Processed and Smallest Batch Size

Products in Blender 3	Batch Size	Selected Batch
Product A	500 kg	
Product D	***250 kg***	Smallest Batch Size
Product E	400 kg	
Products in Mixer 2	**Batch Size**	**Selected Batch**
Product P	125 Liters	
Product Q	200 Liters	
Product T	***100 Liters***	Smallest Batch Size
Products in Tablet Packaging Line 4	Batch Size	Selected Batch
Product A	250 kg	
Product F	***100 kg***	Smallest Batch Size
Product G	150 kg	
Product I	200 kg	
Products in Liquid Filling Line 2	Batch Size	Selected Batch
Product S	75 Liters	
Product T	***50 Liters***	Smallest Batch Size
Product U	100 Liters	

6 tablets a day" or "No more than 3 fl oz per day". If the medication package insert does not contain the MDD it may be necessary to contact the clinician(s) involved in the clinical studies to obtain this value.

5.3.3 Ratios of batch size to daily dose can be calculated in three different ways in 5.3.4.1 – 5.3.4.4.

5.3.4 For investigational medicinal products (IMPs) when the product is manufactured on the equipment, if the subsequent product's MDD is known it can be used in the product's MSC calculation and a limit derived. For IMPs lacking an MDD, a qualified toxicologist and the clinician responsible for the IMP should be consulted to determine an appropriate MDD. Parameters the toxicologist and the clinician may consider include, for example, subject body weight, the HBEL if known, first-in-human doses, maximum tolerated dose, as well as the steepness of the dose-response curve if known. The selection of the MDD should be made on a case-by case basis and requires consideration of all current data for each IMP.

5.3.4.1 *Batch Size / Daily Dose Ratio (BS_Q / DD) using Quantities*—When the batch size is the smallest batch size this refers to the smallest quantity (weight or volume) of the final mix/blend of the subsequent product processed in the equipment/equipment train. The BS_Q can be expressed in kg or L depending on the type of formulation. When the DD is the maximum (daily) dose this refers to the maximum dose of the subsequent product processed in the equipment/equipment train that can be administered in a day. It is generally expressed in mg/day or mL/day.

$$MDD = MNA \times MQ \quad (2)$$

Example calculations are shown in Appendix X1.

5.3.4.2 Where MNA is the maximum number of administrations/applications per day or the maximum number of times a product can be administered per day and MQ is the maximum quantity administered in each dose/application. The MDD used for the calculation of safe limits must include the total weight of the unit dose (weight of API + weight of excipients) and not just the weight of API. Table 2 provides some examples of MNA and MQ values for the different dosage forms.

5.3.4.3 *Batch Size / Daily Dose Ratio using Dosage Units (SBS_{DU}/MNDU)*—SBS_{DU} refers to the smallest number of dosage units manufactured per batch and is expressed in units/batch. MNDU is the maximum number of dosage units administered per day and is expressed in units/day. This ratio is the simplified form of the ratio discussed in 5.3.4.1. It can be used as an alternative to the SBS_Q/M(D)D ratio for the calculation of MSC. The advantage of using this ratio is that it does not require the estimation of weight or volume of a unit dose or the entire batch. For products manufactured/administered in dosage units, the total number of dosage units

TABLE 2 Examples of MNA and MQ for the Different Dosage Forms (21)

Dosage form	MNA	MQ	Example
Solids – single dosage units (for example, tablet, capsule)	The maximum number of dosage units that can be administered in a day (units/day)	The weight of a single unit (mg/unit)	Dosage: One or two capsules orally every 6 to 12 hours. Maximum number of capsules administered per day: 2 units × (24 hours/day ÷ 6 hours) = 8 units/day; Capsule weight: 295 mg/unit; MDD = 295 × 8 = 2360 mg/day
Liquids – oral, injectable	The maximum number of times the product can be administered in a day	The maximum volume administered in a single dose (in mL/dose)	Dosage (cough syrup): 5 mL to 10 mL three or four times a day. Maximum number of times cough syrup administered per day: 4 administration/day; The maximum quantity of a single dose: 10 ml/administration; MDD = 4 × 10 = 40 mL/day Dosage (Injectable): 10 mL four times a day. Maximum number of injections per day: 4 injections/day; The maximum quantity of a single dose: 10 ml/injection; MDD = 4 × 10 = 40 mL/day
Liquids – ophthalmic/otic drops	The maximum number of drops that can be instilled in a day (drops/day)	Volume of a drop (mLs/drop)	Dosage: One or two drops into each eye five (5) times daily. Maximum number of drops instilled per day: 2 drops/application/eye × 2 eye × 5 application/day = 20 drops/day; Volume of one drop: 0.5 mL/drop MDD = 20 × 0.5 = 10 mL/day
Topicals (for example, topical cream, ointment, gel)	The maximum number of applications per day (applications/day)	Amount applied in each application (g/application or mL/application)[A]	Dosage (topical ointment): 3 to 5 times daily with a maximum 2 finger tip units (FTUs) per application (21-23). Maximum number of FTUs per application: 2 FTU/application; Maximum number of applications per day: 5 application/day; Weight of 1 FTU: 0.5 g/FTU; MDD = 2 × 5 × 0.5 = 5 g/day

[A] The maximum quantity per application of many topical formulations (for example, shampoo, lotion, mouthwash) can be obtained from the Scientific Committee on Consumer Safety notes (24).

in a batch can be calculated by dividing the quantity (weight or volume) of the final mix by the quantity of a unit dose. That is,

$$SBS_{DU}(\text{units}/\text{batch}) = SBS_{Q}(\text{mg}/\text{batch} \quad \text{or} \quad \text{mL}/\text{batch}) \div \text{Unit Dose Quantity} \ (\text{mg}/\text{unit} \quad \text{or} \quad \text{mL}/\text{unit}) \tag{3}$$

Example calculations are shown in Appendix X1. This approach is most applicable in packaging operations where batch sizes are typically expressed in dosage units rather than kilograms.

5.3.4.4 *Batch Size / Daily Dose Ratio using API Quantities ($SBS_{Q\text{-}API}$)*—$SBS_{Q\text{-}API}$ refers to the smallest batch size of the API or the smallest batch quantity (weight or volume) of the API produced. This ratio is typically used for calculating the MSC in API manufacturing setting. For finished products, it can be used as an alternative to the ratios discussed in 5.3.4.1 and 5.3.4.3. In the case of drug products, $SBS_{Q\text{-}API}$ refers to the quantity (weight or volume) of the API in the smallest batch size of the final mix of Product B. $SBS_{Q\text{-}API}$ is expressed in kilograms or liters.

5.3.4.5 MDD_{API} is the maximum daily dose of the API and refers to the maximum dose of the API that can be administered daily or in a single (intermittent or lifetime) administration by a particular route of administration. When the information about the route of administration and dosage form of the product for which the API can be used is not available, then the MDD_{API} should be defined based on a formal risk assessment.

5.3.4.6 For finished products, it is the quantity of the API in the maximum daily dose of Product B. It is expressed in mg/day or mL/day. When the maximum daily dose is given in dose per kilogram body-weight (for example, mg/kg-bw/day), it can be converted to the daily dose in mg/day by multiplying the dose by the body-weight (in kilograms) of the population that is expected to receive larger dose of the API. When a finished products consists of multiple APIs, the $SBS_{Q\text{-}API}$ and MDD_{API} values of any API can be used for the calculation of the ratio.

5.3.4.7 *Device / Residue per Device for Medical Devices*—For products (for example, implants) that are not administered on a daily basis, the administered dose should not be scaled-down to a daily dose. In such cases, the HBEL value of the cleaning process residue should be adjusted to a one time exposure over the lifetime of the device and the largest possible patient exposure. For products that are administered on a replicate exposure (multiple times in a day), the administered exposure should not be scaled to a daily exposure. In such cases the value of the cleaning process residue is used as calculated.

5.4 *Maximum Safe Surface Residue (MSSR)*—Because the MSC is the total amount safe to carryover into the next manufactured product, it is also the total amount safe for carryover onto shared equipment surfaces (that is, shared between the cleaned product and the next manufactured product). The maximum safe surface residue (MSSR) is calculated by dividing the MSC by the total shared product contact surface of the equipment between the two products. MSSR, which may be expressed for chemical residues in mass units per surface area (for example, $\mu g/cm^2$), is expressed in the following equation:

$$MSSR = \frac{MSC}{TSSA} \tag{4}$$

5.4.1 *Total Shared Surface Area (TSSA)*—The TSSA is the total area of the equipment that is shared between products. That is, the surface area of a piece of equipment that more than one product comes in contact with during processing.

NOTE 2—Areas identified as risks should be sampled during the validation.

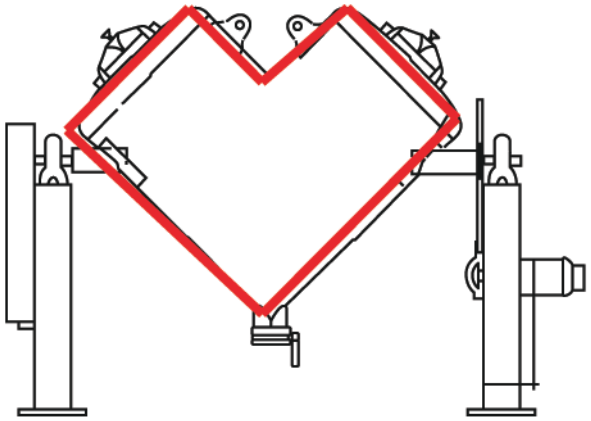
5.4.1.1 An alternative to the TSSA is when the concern is for carryover into a single, or several, unit doses rather than into a full scale batch. This can be a concern for a filler nozzle, or a tablet punch, where the risk of carryover may be primarily at the start of vial filling or tablet compression and concern a single unit dose and not necessarily the entire batch. In these cases the TSSA may be set to the total inner surface area of the filler nozzle or the surface area of the punch head of the tablet punch. The batch size (BS) is then set to the size of the single, or several units being filled or to the weight of the tablet being compressed. In general though, the initial units of a filling batch or compression batch are discarded due to production issues (low fill volume, low tablet weight, etc.) and this analysis may not be critical. However, this analysis addresses whether product residues are an issue for discarding initial units.

5.4.1.2 The MSSR is widely used in cleaning validation programs, such as in cleaning process development/verification/validation studies, analytical method validation, swab/rinse sample recovery studies, as well as for qualification of visual inspection (see Practice E3263).

5.5 *Safe Limit in Analytical Samples*—Once the MSSR is determined, the safe limit in swab or rinse analytical samples can be calculated. It should be noted that some of the sampling

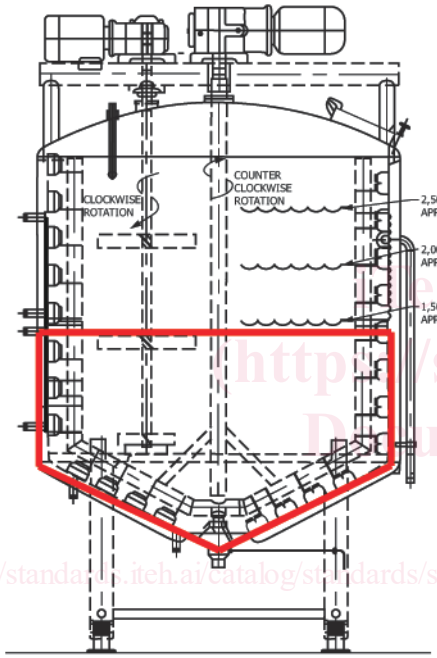
TABLE 3 PDE Values for Class 2 Solvents in Pharmaceutical Products from ICH Q3C

Solvent	PDE (mg/day)	Solvent	PDE (mg/day)
Acetonitrile	4.1	Methanol	30.0
Chlorobenzene	3.6	2-Methoxyethanol	0.5
Chloroform	0.6	Methylbutyl ketone	0.5
Cumene	0.7	Methylcyclohexane	11.8
Cyclohexane	38.8	Methylisobutylketone	45
1,2-Dichloroethene	18.7	N-Methylpyrrolidone	5.3
Dichloromethane	6.0	Nitromethane	0.5
1,2-Dimethoxyethane	1.0	Pyridine	2.0
N,N-Dimethylacetamide	10.9	Sulfolane	1.6
N,N-Dimethylformamide	8.8	Tetrahydrofuran	7.2
1,4-Dioxane	3.8	Tetralin	1.0
2-Ethoxyethanol	1.6	Toluene	8.9
Ethylene Glycol	6.2	1,1,2-Trichloroethene	0.8
Formamide	2.2	Xylene	21.7
Hexane	2.9		



This Blender may have different batch sizes but the product contact area will be the same as every batch will contact all the internal surface area as the blender rotates. All surfaces areas within the red outlined area must be included in the total surface area calculation.

FIG. 2 Example Drawing of ″V″ Blender Showing Product Contact Areas



This Kettle has three different batch sizes but each batch size will have a different product contact area. The 1500 gal batches may not contact the dome and upper areas of the mixer shafts. All surfaces areas within the red outlined area must be included in the total surface area calculation. As a worse case, some companies use the total surface area of the equipment regardless of the batch size but it should be understood that this will lower the safe limits. Although some companies may use these lower surfaces area a risk assessment should be performed to identify any points of concern where cleaning process residues may occur from the areas outside the calculated area (for example, vent valves, vessel penetrations, manways/ manholes, etc.) and how they may contribute to product carryover.

FIG. 3 Example Drawing of Kettle Showing Product Contact Areas

may encompass the entire surface of the sampled equipment or device. Three typical cases of safe limits in samples are covered below.

5.5.1 *Swab Sample Safe Limit*—For swab sampling, the safe limit is expressed as a concentration of the residue in a specified amount of solvent (aqueous or organic) used for extracting the residue from the swab. The concentration limit is typically expressed in units such as µg/mL, ppm, or ppb. This concentration limit is determined by multiplying the MSSR by the area sampled, and then dividing the result by the amount of solvent used for extraction. This is expressed in the following calculation:

$$\text{Swab Sample Safe Limit} = \frac{\text{MSSR} \times \text{SA}}{\text{SDV}} \quad (5)$$

NOTE 3—It is not recommended to include the swab recovery factor in the calculation of swab sample safe limits and the recovery factor should be used to adjust swab data instead (see 5.8).

5.5.1.1 *Swab Area (SA)*—The SA is defined during the swab recovery study. The SA is commonly set to a 5 cm by 5 cm (25 cm^2) area or a 10 cm by 10 cm (100 cm^2) area with a specified swabbing pattern and procedure. This is the size of the area that will be sampled with a swab(s) during the cleaning qualifications. The 25 cm^2 swab areas are becoming more common as many sampling sites required in protocols are smaller than 100 cm^2. Equivalent SAs may be 2 in. by 2 in. (4 $in.^2$) and 4 in. by 4 in. (16 $in.^2$).

NOTE 4—SAs used during qualification studies may be larger or smaller than the SAs defined in the recovery studies but the percent recovery must be also determined for these different sized areas.

5.5.1.2 *Swab Dilution Volume (SDV)*—The SDV used to extract the residues from the swab(s) is defined during the method development study. The SDV can range from as low as 4 mL for some HPLC methods up to 40 mL for TOC methods.

NOTE 5—SDVs used during qualification studies may be larger or smaller than the SDVs defined in the recovery studies but the method would require revision and validation for these different sized volumes.

5.5.2 *Rinse Sample Safe Limit*—For rinse sampling, most companies express the safe limit as a concentration of the residue in a specified amount of the rinse sampling solution. This concentration limit is typically express in units such as µg/mL, ppm, or ppb. This concentration limit is determined the following equation:

$$\text{Rinse Sample Safe Limit}\,(\mu g/mL) = \frac{MSSR \times RA}{RV} \quad (6)$$

5.5.2.1 *Rinse Area (RA)*—The RA is dependent on the area of equipment or device being sampled. The RA could be the total surface area of a small part or the total surface area of an entire tank, vessel or device. The RA could also be a part of the total surface area of a small part or be a part the total surface area of an entire tank, vessel or device.

NOTE 6—There should be a rinse recovery study performed and documented to justify the rinse area and what the RA is.

5.5.2.2 *Rinse Volume (RV)*—The RV is dependent on the rinse area that is being sampled. The RV used must be sufficiently large to adequately recover residues from the total area being sampled, otherwise, the rinse sample will not be representative. In addition, the rinse volume should not be so large as to dilute the sample, making the residues difficult to detect and artificially lowering the safe limits. Therefore the rinse volume should be kept as low as possible. There should be a rinse recovery study performed to justify and document what the rinse volume used should be.

5.5.2.3 *Rinse Volume Determination*—For cleaning validation purposes, two approaches are used for rinse sampling: post-cleaning rinse sampling (also known as analytical rinse sampling) and final rinse sampling.

NOTE 7—Rinse sampling applies to residues that are extraneous to the product (for example, cleaning agents) and not to sampling for extractables and leachables (see ISO 10993-12 for guidance).

5.5.2.4 In post-cleaning rinse sampling, after the completion of the cleaning cycle (including drying) of the surface (to be sampled), an additional rinse of the surface, with a pre-set volume, is carried out. Samples of the additional rinse are collected to test for the cleaning process residue(s). In this sampling an optimal rinse volume should be determined in relation to rinsing parameters that can cover the entire surface to be sampled and effectively recover the residue.

5.5.2.5 In final rinse sampling, samples from the final rinse step of the cleaning cycle are collected to test for the cleaning process residue(s). A final rinse is the last step (before drying step) of the cleaning cycle and is meant to remove any last traces of cleaning process residues. Hence, final rinse sampling assumes that if the final rinse sample meets the acceptance criteria, then a post-cleaning rinse should also meet the criteria.

5.5.2.6 Where final rinse sampling is used the cleaning cycle should have consistent and known rinse (or range of) volumes otherwise the cleaning is not consistent and cannot be considered validated. Final rinse sampling should be considered instead for qualification as a process analytical technology (PAT) application. In a qualified PAT based system (for example, conductivity, TOC sensors), final rinse samples are not taken as the sensor readout is used as the rinse endpoint (see Guide E2476).

5.5.2.7 The rinse volume selected for sampling should ensure that the residue concentration levels are above quantitation limits of the analytical technique used. As the rinse limit is inversely proportional to the rinse volume (that is, the higher the rinse volume, the lower the limit), selecting a large volume for rinsing would result in lower concentration levels that will be below the quantitation limits of many analytical methods. This may require developing a highly sensitive analytical method for the measurement of the residue. In some cases, the rinse sample can be concentrated (for example, rotary evaporation, etc.) to meet the limits of quantitation. Selection of the rinse volume depends on the surface area of the equipment/medical device to be rinsed, the quantitation limit of the analytical method used and the % recovery of the residue by rinse sampling. The following are some examples of estimating the rinse volume.

5.5.2.8 *Based on Volume-to-Surface Area Ratio*—When the information about the volume needed to fully cover the sample area (also known as volume-to-surface area ratio or VSR) of a surface is available, then from this information, the rinse volume can be estimated by multiplying the value by the surface area of the surface to be rinsed. That is,

$$RV = VSR \times RA \quad (7)$$

where:

RV = rinse volume (in mL),
VSR = volume-to-surface area ratio (in mL/in.^{2}, mL/cm^2), and
RA = rinse sample area (in in.^{2}, cm^2).

5.5.2.9 When the VSR is not known, then this ratio can be determined from small-scale studies (for example, recovery studies), sprayball coverage study or experience with cleaning of similar equipment. The following example shows how to determine the VSR using data from an acceptable rinse recovery study.

Coupon surface area	= 25 cm^2
Rinse volume used for study	= 50 mL
VSR	= 50 mL / 25 cm^2 = 2 mL/cm^2
VSR	= 2 mL/cm^2
Rinse sample area	= 10 000 cm^2
Rinse volume	= 20 000 mL

For a medical device, the volume used for the rinse recovery study should be used.

5.5.2.10 *Based on the Solubility of the Residue*—When the solubility of the target cleaning process residue is known the volume of solution needed to dissolve the expected quantity of the cleaning process residue can be estimated from the solubility information. For example, if the solubility of a solute is 2 mg/mL, then to fully dissolve 50 mg, a volume of 25 mL of solvent will be needed.

5.5.2.11 Since the exact quantity of cleaning process residues remaining on equipment surface after cleaning is not known, then the volume needed to dissolve a cleaning process residue at its MSSR limit can be used. The minimal volume needed can be estimated by dividing the MSSR value of the