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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.

~~ε[1] NOTE—Corrections were made editorially to 3.1.13 in October 2018.~~

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);~~ (APIs)); all dosage forms; ~~and over-the-counter, veterinary, biologics, and clinical supplies)~~ 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~~ 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 ~~14698).~~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

[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.

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 ~~Standards:~~Guidelines:*[4]

Q8 Pharmaceutical Development
Q9 Quality Risk Management
Q10 Pharmaceutical Quality System
Q11 Development and Manufacture of Drug Substances
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 ~~Standards:~~Regulations:*[6]

21 CFR 211.67 ~~Equipment~~ 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

[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.
[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. 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~~ 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 *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.~~

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

3.1.3 *clean-in-place, CIP, n*—~~method of cleaning~~ 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~~ equipment, product, or ~~product.~~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).

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, ~~temperature, time, and so forth.~~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**

~~3.1.14 *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.~~

3.1.17 *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 non-linearity.

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*—~~strategy~~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 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 ~~equipment,~~ 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.

~~3.1.20 *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).~~

3.1.27 *maximum ~~allowable carryover, MAC or MACO,~~ daily dose, MDD, n*—~~maximum amount of carryover from one product to the next.~~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*—

~~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).~~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 ~~ADE~~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.

3.1.29 *maximum safe surface residue, MSSR, n*—maximum amount of process residue that can remain on equipment surfaces or devices and still be safe to patients.

3.1.29.1 *Discussion*—

The MSSR is mathematically calculated dividing the maximum safe carryover (MSC) by the total area of contact (MSC/total equipment surface area). The MSSR is not used as a limit and is only used for risk assessment. The comparison of process residues to MSSRs can demonstrate whether the process residues on equipment product contact surfaces pose significant risk to patients and shows what the margin of safety is for that process residue.

3.1.30 *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.

3.1.30.1 *Discussion*—

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

3.1.31 *probability, n*—likelihood of occurrence of harm. **ICH Q9**

3.1.32 *process capability, n*—statistical estimate of the outcome of a characteristic from a process that has been demonstrated to be in a state of statistical control. **E2281**

3.1.33 ~~*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.

3.1.33.1 *Discussion*—

Guide F3127 defines residue as 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 as contamination by environmental factors (adsorbates).

~~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.~~

3.1.34 *qualified* ~~*toxicologist/pharmacologist,*~~*expert, n*—individual with specific education and training in ~~toxicology/pharmacology~~ toxicology/pharmacology/pharmacotherapy and risk assessment methods that can apply the principles of toxicology to deriving an ~~ADE or PDE value for required process residues.~~ HBEL. **E3219**

3.1.34.1 *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). For medical devices, this person should be familiar with medical devices and the determination of HBEL.

3.1.35 *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**

3.1.36 ~~*representative*~~ *surrogate 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.~~part that is used as a substitute for a piece of manufacturing equipment or a medical device surface.

3.1.37 *visual inspection, VI, 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. **E3263**

3.1.38 *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. **E3263**

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 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~~ CFMEA 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~~ 82, 4**). If criticality of the medical device is known, then cleaning failure modes effects and criticality analysis (CFMECA) may be used.

3.2.3 *cleaning process capability score, n*—value obtained by taking the reciprocal of the process capability index (upper) and multiplying by 10 (**2**).

3.2.4 *statistical subject matter expert, n*—individual with a working knowledge and education, training, or experience in statistics who can apply statistical analysis to data from cleaning and cleaning validation studies.

3.2.5 *recovery study, n*—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.

3.2.5.1 *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.

3.2.6 *toxicity score, n*—value obtained by taking their negative logarithm of the HBEL (in units of grams per day) (**4**).

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~~**).) and Quality Management Maturity for Finished Dosage Forms Pilot Program for Domestic Drug Product Manufacturers; Program Announcement.

4.3 This guide supports, and is consistent with, elements from ICH Q8, ICH Q9, ICH Q10, ICH Q11, and ICH ~~Q11.~~Q12.

4.4 This guide supports and is consistent with the content and intent of ISO 14971.

4.5 *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~~ improvement, and (*6*) life-cycle management as described in the ICH Q series.

5. ~~Science-Based, Risk-Based,~~Science-, Risk-, 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: risk = *f* (toxicity of process residues, exposure to process residues, and detectability of process residues).

6.4 Fig. 1 shows the continuum of risk in cleaning as a function of the toxicity of process residues, the level of potential exposure to the process residues and the detectability of the process residues (**5**).

6.5 Fig. 2 shows the continuum of risk in cleaning as a function of the criticality for medical device manufacturing.

6.6 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, process aids, bioburden/endotoxin, and so forth), the ability of a cleaning process to remove process residues from manufacturing equipment or medical devices to levels that are acceptable, and the ability to detect and quantify the presence of process residues after cleaning and in the case of medical devices, the level of its criticality.

7. Risk (Hazard) Identification

7.1 Risk identification should encompass the identification of process residue hazards, equipment design hazards, and procedural hazards.

7.2 *Chemical Hazard Identification*—The hazard presented by a potential process residue may be determined from a toxicological review performed by a qualified expert. This involves a thorough review of all relevant toxicological data available for the process residue under study. When preclinical and clinical data on APIs are available to review, an HBEL can be determined and used as a measure of the hazard presented by a compound (Guide E3219).

7.2.1 HBELs are used to calculate MSCs, MSSRs, and swab and rinse limits for use in risk evaluation. See 9.4.4 for setting limits based on SPC.

7.2.2 Chemicals identified as process residues that are known hazards should be scheduled for elimination or remediation steps.

7.3 *Microbiological Hazard Identification*—The hazard of possible bioburden from a previous product or cleaning process and the possibility of microbial proliferation after a cleaning process and the hazards this presents, including the need for subsequent disinfection, should be considered. For example, microbiological hazard(s) presented by holding equipment either in a dirty state or in clean state should be considered. The impact of bioburden levels on subsequent sterilization or endotoxin and the need for subsequent depyrogenation should be considered.

7.3.1 Microbiological agents identified as process residues that are known hazards should be scheduled for elimination or remediation steps.

7.4 *Equipment Design Hazard Identification*—The potential hazards presented by equipment design should also be considered,

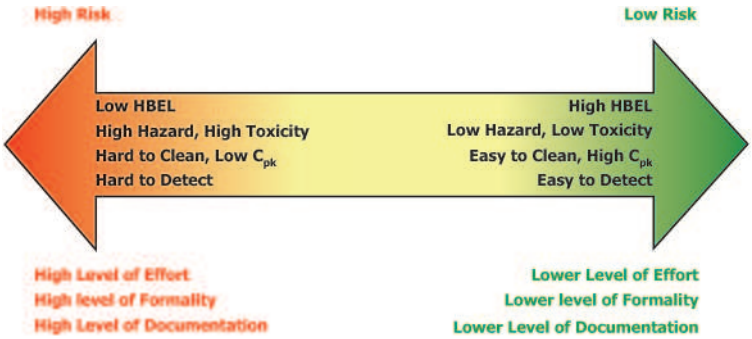
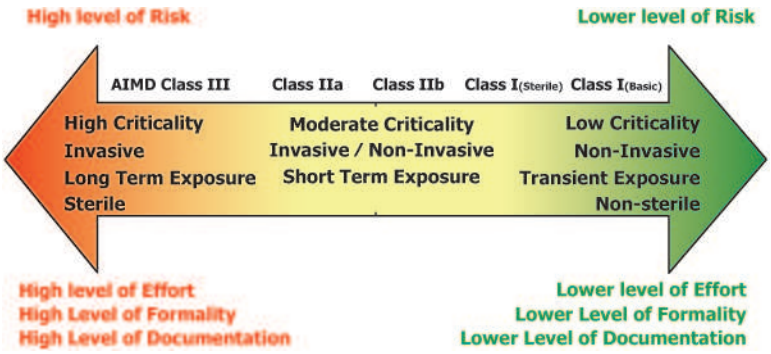


FIG. 1 Continuum of Cleaning Risk based on Toxicity, Exposure, and Detectability



Med devices follow FDA Definitions and ISO of Med Device Classes to determine level of risk to patient.

FIG. 2 Continuum of Medical Device Risk

such as the possibility of product buildup. Equipment should be designed to facilitate cleaning, inspection, and monitoring. Cleanability should be a requirement in User Requirement Specifications prior to purchase of equipment, including determination of Materials of Construction of product contact surfaces, instructions on disassembly, and equipment manufacturer's recommendation on cleaning.

7.4.1 Equipment designs identified as known hazards should be scheduled for elimination or remediation steps.

7.5 *Procedural Hazard Identification*—During development and before use, cleaning procedures should be analyzed using a risk assessment, 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. Legacy cleaning procedures should also be subjected to risk assessments to minimize the risk of cleaning failures, including review of legacy cleaning data.

7.5.1 Procedural steps identified as known hazards should be scheduled for elimination or remediation steps.

8. Risk ~~Assessment~~Analysis

~~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.~~

8.1 ~~*Risk Identification*—~~Risk ~~identification should encompass the identification of~~ analysis is the estimation of the risk associated with the identified hazards in Section 7~~process residue hazards, equipment design hazards, and procedural hazards.~~ and is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms.

~~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 (9). 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*(9).~~

~~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 (9, 10). 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 (11, 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 (13). 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, 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.~~

8.2 After identifying the hazards posed in Section 7, the risks associated with them should be analyzed. This risk analysis should involve the cleaning process development, facility/equipment design review, cleaning procedure review (including legacy cleaning data review), and the selection of analytical methods. The analysis should also determine what steps can be taken to mitigate the identified risks.

8.3 The risk analysis should focus on how cleaning may affect the patient safety and quality of the next product or device functionality.

8.4 The impact of the different factors (process residue cleanability (Test Method G122), cleaning/rinsing agents, equipment engineering, and so forth) that have an impact on the outcome of the cleaning process should be analyzed.

8.5 ~~*Risk Analysis:*~~ The cleaning process risk analysis is used to determine the necessary cleaning qualifications and identify appropriate risk control mechanisms.

~~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.~~

8.5.1 *Process Residue Characterization:*

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

(1) Cleanability should be demonstrated through bench scale testing (Practice G121 and Test Method G122). In the case of API manufacturing, the solubility of the active in the process solvent may be used as a measure of cleanability.

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

8.5.2 *Equipment Design for Cleanability:*

8.5.2.1 The design of equipment has a critical impact on its cleanability. User Requirement Specifications (URS) for equipment design should include requirements for the equipment to be cleanable as per 21CFR21 such as material of construction, total surface areas, manufacturer's suggested cleaning procedures, and so forth (Guides E2500 and F3127). These specifications should be considered before purchase.

(1) Guide F3357 has useful guidance on designing medical devices for cleanability.

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

8.5.2.3 Where ~~satisfactory~~ equipment design is not found to be satisfactory in the risk (hazard) identification stage, or where cleaning results cannot be achieved because of limitations in the equipment design, the equipment may need to be modified, dedicated, or replaced.

8.5.3 *Evaluation of ~~Historical~~Legacy 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~~the 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). This evaluation should include statistical analysis of the data.

8.5.3.1 These legacy data can also be used to facilitate new product introduction including evaluation of new product HBELs for acceptability into the facility. (HBEL-based acceptance limit calculations can be found in 8.6.2.)

8.5.4 ~~*Levels of Cleaning—Degree of Cleaning Based on Risk*~~—Manufacturing equipment may require different ~~levels~~degrees of cleaning ~~and validation~~ effort, formality and documentation for and validation based on the level of risk under different circumstances. To determine the appropriate ~~cleaning level,~~ degree of cleaning, 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~~ different types of cleaning based on the level of risk, for example:

8.5.4.1 Cleaning between different products,

8.5.4.2 Cleaning between similar products,

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

8.5.4.4 Cleaning of dedicated equipment,

8.5.4.5 Cleaning after equipment maintenance,

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

8.5.4.7 Cleaning after ~~sampling,~~ sampling (for example, environmental monitoring or cleaning validation), and

8.5.4.8 Cleaning after non-routine ~~operations.~~operations (for example, placebo runs during equipment qualifications).

8.5.5 *Cleaning Process Development*—Cleaning processes should ~~not be adopted randomly or chosen~~ be developed for each individual product to provide optimal cleaning and not simply adopted based on past ~~use.~~ use (unless demonstrated). Cleaning