Designation: E3263 – 22ε1

Standard Practice for Qualification of Visual Inspection of Pharmaceutical Manufacturing Equipment and Medical Devices for Residues[1]

This standard is issued under the fixed designation E3263; 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—Editorial changes were made to Table 1 (Note 1) in February 2023.

1. Scope

1.1 This practice provides statistically valid procedures for determining the visual detection limit of residues and the qualification of inspectors to perform the visual inspection of pharmaceutical manufacturing equipment surfaces and medical devices for residues.

1.2 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.

1.3 This practice applies to many types of chemical residues (including APIs, intermediates, cleaning agents, processing aids, machining oils, and so forth) that could remain on manufacturing equipment surfaces or medical devices that have undergone all manufacturing steps including cleaning.

1.4 This practice applies only to equipment or devices that have been justified through a Quality Risk Management program to have an acceptable hazard analysis, have cleaning processes that are repeatable and validated and where Visual Inspection can be relied upon to determine the cleanliness of the equipment at the residue limit justified by the HBEL.

1.5 The values stated in International System of Units (SI) units are to be regarded as standard. No other units of measurement are included in this standard.

1.6 *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.*

1.7 *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:*[2]

E2782 Guide for Measurement Systems Analysis (MSA)

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

E3219 Guide for Derivation of Health-Based Exposure Limits (HBELs)

G121 Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents

2.2 *ICH Guidance:*[3]

Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

Q9 Quality Risk Management

Q10 Pharmaceutical Quality System

2.3 *ISO Standard:*[4]

EN 12464 Light and lighting—Lighting of workplaces—Indoor workplaces

2.4 *Federal Regulation:*

21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceuticals[5]

[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 E55.03 on General Pharmaceutical Standards.

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[2] 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.

[3] 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.

[4] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.

[5] Available from U.S. Government Printing Office, Superintendent of Documents, 732 N. Capitol St., NW, Washington, DC 20401-0001, http://www.access.gpo.gov.

2.5 *European Guidance:*

EudraLex Volume 4 Guidelines for Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation[6]

2.6 *U.S. FDA Guidance:*[7]

Guide to Inspections Validation of Cleaning Processes

Guidance for Industry Process Validation: General Principles and Practices

Guidance for Industry PAT A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Guidance for Industry Data Integrity and Compliant with Drug CGMP Questions and Answers

3. Terminology

3.1 *Definitions:*

3.1.1 *ALCOA, n*—an acronym referring to data, whether paper or electronic, requiring data to be Attributable, Legible, Contemporaneous, Original and Accurate, as defined in U.S. FDA guidance.

3.1.2 *cleaning process residue, n*—any residue, including, but not limited to, active pharmaceutical ingredients (APIs), cleaning agents, degradation products, intermediates, excipients, and microbes remaining after a cleaning process.

3.1.3 *cleaning qualification, n*—the risk evaluation activities of the cleaning process during Stage 2 of the Cleaning Validation Lifecycle. Lifecycle verifications provide assurance that during routine production the cleaning process is, or remains, in a state of control.

3.1.4 *cleaning validation, n*—collection and evaluation of data from the cleaning process design stage through cleaning at commercial scale that establishes scientific evidence that a cleaning process is capable of consistently delivering clean equipment; lifecycle verifications provide assurance that during routine production the cleaning process is, or remains, in a state of control.

3.1.5 *data integrity, n*—data integrity refers to the completeness, consistency, and accuracy of data.

3.1.5.1 *Discussion*—Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate.

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

3.1.6.1 *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).

3.1.7 *health-based exposure limit, HBEL, n*—dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime.

3.1.7.1 *Discussion*—The HBEL, being based on the critical effect, should be protective of all populations by all routes of administration and the result of a structured scientific evaluation of all available pharmacological and toxicological data including both nonclinical and clinical data. **E3219**

3.1.8 *lumen, n*—SI unit of luminous flux and is the luminous flux emitted within a solid angle of 1 steradian by a point source having a uniform intensity of 1 cd.

3.1.8.1 *Discussion*—As the lumen is a measure of energy per unit time, it shall also be related to the watt.

3.1.9 *lux, lx, n*—unit of illuminance is equal to the illumination produced by a luminous flux of 1 lumen distributed uniformly over an area of 1 m^2.

3.1.9.1 *Discussion*—It can also be described as the illumination on a surface, all points of which are at a distance of 1 m from a point source of 1 candela (cd).

3.1.10 *margin of safety, n*—difference between the cleaning acceptance limit (based on an 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 by a number of ways, including the process capability index (Cpk) and the process performance index (Ppk).

3.1.11 *maximum safe carryover, MSC, n*—maximum amount of carryover of a residual process residue (for example, API, cleaning agent, degradant) into the next product manufactured without presenting an appreciable health risk to patients.

3.1.11.1 *Discussion*—The MSC is calculated from the HBEL and the total number of doses in a subsequent batch or into the next manufacturing step, including the final step.

3.1.12 *maximum safe surface residue, MSSR, n*—maximum amount of residual 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.

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

3.1.13 *probability, n*—likelihood of occurrence of harm.

3.1.14 *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. **E3219, 21 CFR 211.25(a), and 21 CFR 211.34**

3.1.15 *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. **E3106**

3.2 *Definitions of Terms Specific to This Standard:*

[6] Available from https://ec.europa.eu/health/documents/eudralex/vol-4_en.

[7] Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, http://www.fda.gov.