



Designation: ~~E3263 – 20~~ E3263 – 22

Standard Practice for Qualification of Visual Inspection of Pharmaceutical Manufacturing Equipment and Medical Devices for Residues¹

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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~~ (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 ~~a~~ 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 ~~SI~~ 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.*

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. 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](#)

[ICH-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 211.67211 Equipment Cleaning and Maintenance](#) [Current Good Manufacturing Practice for Finished Pharmaceuticals](#)⁵

2.5 European Regulation: 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 Standard: 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](#)

iTeh Standards (<https://standards.iteh.ai>) Document Preview

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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>.

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

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 *cleaning verification, data integrity, n*—confirmation, through the provision of objective evidence, that specified cleaning requirements have been fulfilled.~~ 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.

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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 m².

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 $\mu\text{g}/\text{cm}^2$, $\text{mg}/\text{in.}^2$, 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.

3.1.13 *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:*

3.2.1 *attribute agreement analysis, n*—assessment of the agreement between the ratings made by inspectors and the known standards.

3.2.1.1 *Discussion*—

Attribute agreement analysis can be used to determine the accuracy of the assessments made by inspectors and identify which items have the highest misclassification rates.

3.2.2 *compound, n—in this practice*, this term may be either the active pharmaceutical ingredient (API) that is used in the formulation of a pharmaceutical product or a cleaning agent used to remove residues from equipment or devices.

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3.2.3 *degradant, n*—product of the breakdown of a molecule through a degradation process. [08e63d073/astm-e3263-22](https://standards.iteh.ai/ASTM/E3263-22)

3.2.4 *degradation, n*—gradual decomposition of a molecule in which it is reduced in molecular size in small steps.

Encyclopedia of Chemistry (1)⁸

3.2.5 *product, n—in this practice*, this term includes pharmaceutical formulations or medical devices used for the qualification of visual inspection.

3.2.6 *qualification, n*—operation aimed at proving with regard to equipment, material, or personnel that the required conditions actually provide the expected results.

3.2.7 *spike, n*—known amount of a solution of a compound/product/residue that is applied to a surrogate surface or device for use in a qualification study.

3.2.7.1 *Discussion*—

The act of applying these solutions is termed “spiking” and the surrogate surface or device that the solution is applied to is referred to a “spiked” surrogate surface or device.

3.2.8 *surrogate surface, n*—part that is used as a substitute for a piece of manufacturing equipment or a medical device surface.

3.2.8.1 *Discussion*—

These are fabricated parts made of the same material of construction (MOC) and surface finish as the manufacturing equipment

⁸ The boldface numbers in parentheses refer to a list of references at the end of this standard.

or the medical device surface. Some commonly used surrogate surfaces are called “coupons,” which are square or rectangular pieces (for example, 5 × 5 cm, 10 × 10 cm, 4 × 4 in., and so forth) of the manufacturing equipment or medical device MOC. Some surrogate surfaces are actual samples of the medical devices themselves or smaller pieces of the manufacturing equipment used to represent larger pieces of the manufacturing equipment or medical device.

3.2.9 *visual detection index, VDI, n*—logarithm of the ratio on the visual residue limit divided by the maximum safe surface residue.

3.2.9.1 *Discussion*—

The log of this ratio obtains a logarithmic scale that equals “0” when the values of the MSSR and visual residue limit (VRL) are equal and becomes negative when the VRL is lower than the MSSR and positive when it is higher. This scale provides a simple and visual means of evaluating whether a VRL is low enough to be justified for visual inspection.

3.2.10 *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.

3.2.10.1 *Discussion*—

Supplementary aids, such as a boroscope, enable inspection for residues in hard-to-reach areas (for example, piping) may be included as part of the visual inspection.

3.2.11 *visual residue limit, VRL, n*—lowest level of a residue on a surface (in $\mu\text{g}/\text{cm}^2$ or mg/m^2) that is visible to a qualified inspector under defined viewing conditions.

4. Significance and Use

4.1 Application of the approach described within this practice applies the science-based, risk-based, and statistics-based concepts and principles introduced in Guides [E3106](#) and [E3219](#).

4.2 Application of the approach described within this practice provides a science-, risk-, and statistical-based approach for qualifying the inspection of equipment for cleanliness in accordance with 21 CFR ~~211.67(b)(6)~~. 211.67(b)(6) and is in accordance with FDA Process Validation Guidance Life Cycle approach.

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4.3 Application of the approach described within this practice provides a science-, risk-, and statistical-based approach for qualifying the visual inspection of equipment for cleanliness in accordance with European Medicines Agency (EMA) Annex ~~15~~ 15.(2).

4.4 Application of the approach described within this practice provides a science-, risk-, and statistical-based approach for qualifying the visual inspection of equipment for cleanliness in accordance with the EMA’s Q&A Guidance (Q&A’s #7 and #8) (2).

4.5 Visual Inspection used as described in 4.4 should only be used in situations where there is a suitable safety margin between the VRL and MSSR and robust detectability at the VRL.

4.6 Application of the approach described within this practice applies the risk-based concepts and principles introduced in ICH Q9. As stated in ICH Q9, the level of effort, formality, and documentation for validation (including cleaning validation) should also be commensurate with the level of risk.

4.7 Application of the approach described within this practice provides a science-, risk-, and statistical-based approach for releasing manufacturing equipment and manufactured medical devices or cleanliness that is compatible with the U.S. FDA Guidance ~~on Process Analytical Technology Initiative for Industry, PAT – A (Framework 3)~~. for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.

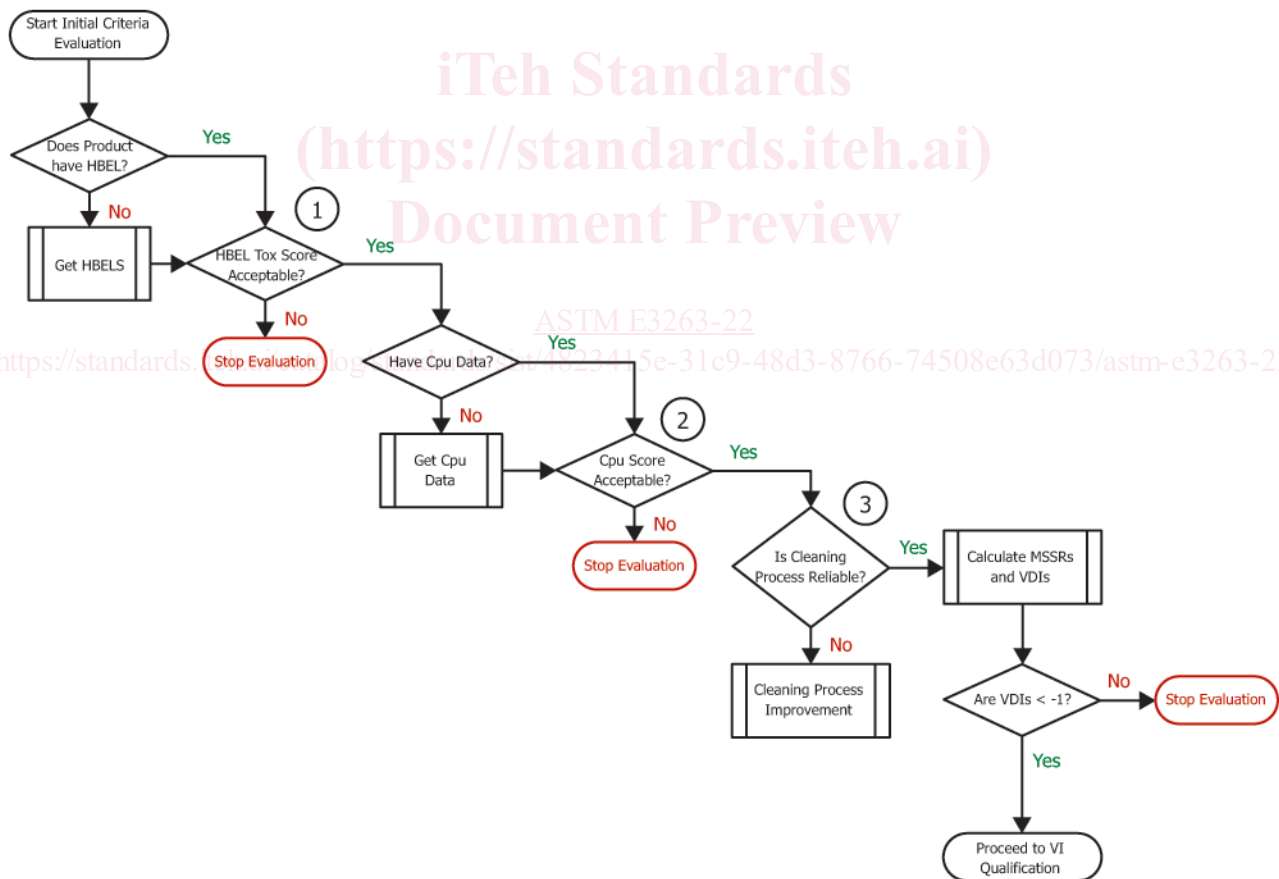
4.8 *Key Concepts*—This practice applies the following key concepts: (1) visual inspection, (2) quality risk management, (3) science-based approach, (4) statistics-based approach, and (5) process knowledge and understanding.

5. Procedure

5.1 U.S. Regulation 21 CFR 211.67 (b) has required the “inspection of manufacturing equipment immediately before use” since 1979. In practice, general, pharmaceutical manufacturers have been releasing equipment some equipment and some compounds based on a “visual” inspection for many years and the industry and regulators have has come to see this “inspection” as a “visual inspection” requirement. However, based on the science, visual inspection may not be appropriate in all circumstances. PIC/S (43) states that “spiking studies should determine the concentration at which most active ingredients are visible,” but there have been only a few studies on VI performed in the past with varying results. In 1993, an article was published that mentioned that spiking studies indicated many compounds were visible at approximately 100 µg/4 in.² (or 4 µg/cm²) (54). Another article claimed that residues can be seen down to 1 µg/cm² by using an additional light source (35). Another article claimed to see residues of several compounds down to approximately 0.4-0.4 µg µg/cm² (6). A series of studies found a range of 0.4 to >10 µg/cm µg/cm² for several different compounds (7 and 87, 8). Studies using a different spiking technique calculated detection limits for one residue at levels of 3, 5, and 7 µg/cm² depending on training (9). A logistic-regression-based approach has also been proposed to derive the limit of visible residue from spiking studies (10).

5.2 Initial Criteria for Establishing Qualification Programs for VI:

5.2.1 The following criteria for the release of equipment without analytical testing (after cleaning qualification is completed) are derived from EMA regulation/guidance and apply to the use of this practice (2). These same criteria are appropriate for qualifying VI for the validation of cleaning processes for pharmaceuticals and medical devices after appropriate justification (11). See Fig. 1 for an example flow diagram of this process.



NOTE 1—In this example, nine out of ten inspectors scored MoC C (probability = 0.9) and only one out of ten inspectors scored MoC D (probability = 0.1) as the hardest-to-see. HBEL Toxicity Scores are calculated as in Reference of (12), the seven materials of construction. None of the other coupons were ranked as the hardest-to-see. Cpu Scores are calculated as in Reference (probability (13), = 0.0). The residue on MoC C is, therefore, selected for the VRL determination as the hardest-to-see residue. Companies should determine what Toxicity Scores and Cpu Scores are acceptable in their organizations. Cleaning process reliability should be demonstrated through review and analysis of swab/rinse data (e.g., Statistical Process Control) and the history of cleaning including any cleaning failures.

FIG. X1.11 Probability Scores for the Ordering of Hardest-to-See Material of Construction Example Flow Diagram for Initial Screening of Candidates for Visual Inspection

5.2.1.1 The compounds/products/residues selected for evaluation of VI shall have acceptable hazard levels based on their HBELs. ~~The visible residue level of the HBELs derived by a qualified expert. See 9.3 compounds/products/residues should be below their MSSRs to be fit for the purpose of VI. (12).~~

5.2.1.2 The cleaning processes of the compounds/products/residues selected should be ~~repeatable~~ validated and not present any significant concerns for patient ~~safety~~. safety if Visual Inspection will be used for release of equipment with no additional analytical testing.

5.2.1.3 The hazard level of a compound/product and the acceptability of the cleaning process should be evaluated to determine acceptability using a risk management tool such as the Shirokizawa Matrix (14).

5.2.1.4 The VI data collected for these compounds/products/residues shall demonstrate that VI can be relied on for determining the cleanliness of the equipment at the residue limit(s) justified by the HBEL.

5.2.2 The design of the equipment/device has an impact on its inspection. Equipment/device design should be considered as ~~part one element of the decision process~~ Risk Assessment (Hazard Identification) taking into consideration the ability of the inspector to inspect the equipment/device easily and adequately.

5.2.2.1 Based on their design, some equipment may not be appropriate for VI.

5.2.2.2 When satisfactory cleaning results cannot be reproducibly achieved because of limitations in the equipment/device, the design of the equipment/device may need to be modified or replaced before VI can be considered. If the equipment/device cannot be modified or replaced, then VI is inappropriate.

5.2.3 The history of cleanings with an evaluation of the historical cleaning data (along with any deviations, investigations, and corrective actions) should be reviewed. Products with a significant history of cleaning failures may not be appropriate for using only VI unless justified through a risk assessment as described in Guide reviewed and the products selected for using VI only justified if the risk assessment provides a valid basis. ~~E3106.~~

5.2.4 If the initial criteria in 5.2 have been met and documented as part of the risk assessment, then the following steps are required next to demonstrate that VI can be relied on for determining the cleanliness of the equipment at the residue limit justified by the HBEL as required in 5.2.1.3.

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5.3 Calculation of MSSR:

5.3.1 The MSSR for each product shall be calculated and is compared with the VRL. The VRL shall be below the MSSR for visual inspection to be acceptable for that product.

5.3.1.1 The MSSR is derived from the HBEL, which is 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. Therefore, the MSSR is a residue level that is safe.

5.3.2 The MSSR, expressed in mass units per surface area (for example, $\mu\text{g}/\text{cm}^2$), is calculated using (Guide E3106):

$$\text{MSSR} = \frac{\text{MSC}}{\text{TSA}} \quad (1)$$

where:

MSSR = maximum safe surface residue (on shared equipment surfaces or the medical device),

MSC = maximum safe carryover, and

TSA = total surface area (of shared equipment surfaces or the medical device).

5.3.3 ~~The MSSRs for all products or residues~~ process residues identified as hazards (Guide E3106) should be determined.

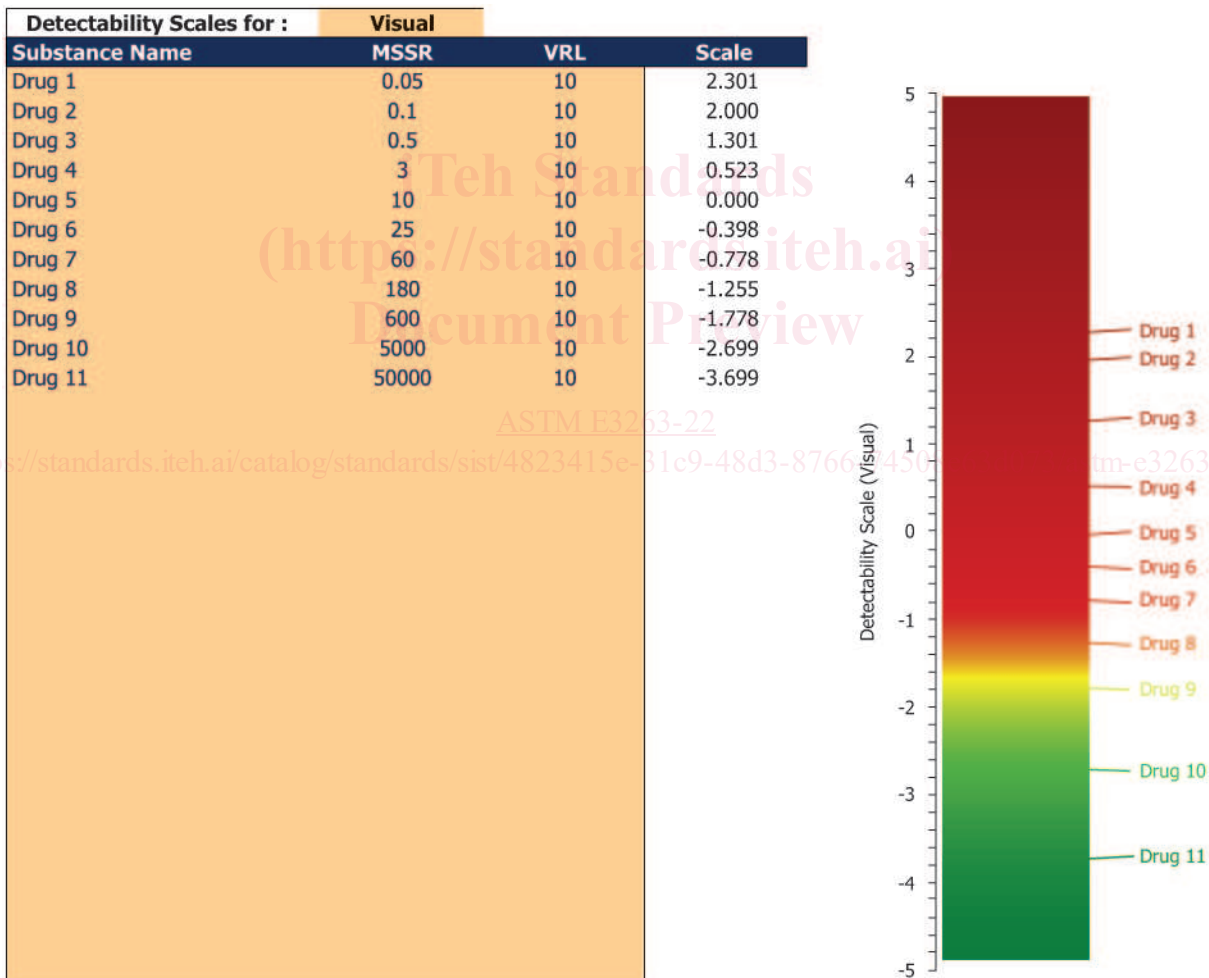
5.3.4 ~~The acceptability of the residues for VI can be measured by using the VDI. The required level below the VDI should be determined by the individual company based on the level of risk. Companies should select how close to a VDI of 0 they believe is justifiable before allowing visual inspection to be used.~~ Visual Detection Index (VDI) (1215).

5.3.4.1 The VDI is determined from the ratio of the MSSR of the residue and the VRL of that residue. By taking the log of this ratio, a value is obtained that equals 0 when the values of the MSSR and VRL are equal, becomes negative when the VRL is lower than the MSSR, and positive when it is higher (15).

5.3.4.2 The VDI is calculated as shown:

$$VDI = \log \frac{VRL}{MSSR} \quad (2)$$

5.3.4.3 The VDI can be used to screen residues for potential candidates for VI. Companies should consider a VDI that is valid and provides assurance that residues can be reliably and consistently detected. An minimum limit for the VDI of -1 is suggested. Values closer to 0 may be acceptable if statistically justified. If all the residues have a VDI of less than -1, then all of them are appropriate candidates for VI. If all the residues have a VDI of greater than -1 then none of them would be appropriate for VI. If the VRLs of the residues are unknown, a simple screening of the calculated MSSRs using a very conservative, "worst case" VRL of 10 µg/cm² could be used. 10 µg/cm² is one of the highest VRLs reported in the literature (7) and residues that had a VDI less than -1 would be very strong candidates for VI. Fig. 2 shows an evaluation of eleven (11) drugs using the VDI for determining whether any of them are suitable for visual inspection.



NOTE 1—In this example, nine out of ten inspectors the MSSRs for eleven (11) drugs have been calculated based on their HBELs and compared to a VRL of 10 µg/cm² scored Coupon C (probability = 0.9) and only one out of ten inspectors scored Coupon D (probability = 0.1) as the hardest-to-see of the seven coupons. None of the other coupons were ranked as the hardest-to-see (probability = 0.0). The residue on Coupon C. Based on this conservative VRL, Drugs 1 to 4 would not be considered candidates for visual inspection studies. Drug 5 to 7 have VDIs of 0 to -0.778 and would also not be considered. Drugs 8 to 11 have VDIs greater than -1 and would be considered appropriate candidates. (Note: if actual VRLs are lower (e.g., 1 mcg/cm² is, therefore, selected for the VRL determination as the hardest-to-see residue.) then more drugs may be candidates).

FIG. X2.12 Probability Scores for the Ordering of Hardest-to-See Residue Using the VDI as a Screening Tool for Candidates for Visual Inspection

5.3.4.4 It should be understood that $10 \mu\text{g}/\text{cm}^2$ is a “worst case” value for the VRL and most residues should have VRLs that are much lower. This exercise can be repeated using other VRLs (e.g., $5 \mu\text{g}/\text{cm}^2$, $1 \mu\text{g}/\text{cm}^2$, etc.) to determine what VRL levels would be required to support VI for the residues. Such screenings can provide guidance on which product are acceptable candidates for visual inspection. (See [Appendix X1](#) for a flow diagram of this screening process.)

5.4 *Viewing (Lighting) Conditions:*

5.4.1 The effect of light and lighting levels on the visual inspection should be known and understood from the qualification studies throughout the lifecycle process of the cleaning validation program.

5.4.2 VI shall be performed under specified conditions. See [Note 1](#).

NOTE 1—Experiments have shown that light levels, viewing angles, and distances are not necessarily critical parameters (16). The human eye is capable of rapid adaptation to changing light levels over a very wide range of intensities, and the eye adapts to minor differences in light levels almost instantaneously and unnoticeably (17). Therefore, minor changes in light levels, distance, or the angle of viewing during inspection may have little impact on the ability to inspect successfully. Some studies have been performed showing no differences in inspection when light levels are between 200–1400 lux (8). These levels are typical of standard indoor lighting of 500–1000 lux (EN-12464).

5.4.2.1 Examples of inspection conditions may be between light level of $>X$, viewing angles of between A and B, and distances of $<Z$.

5.4.3 Qualification studies are best performed in the manufacturing or inspection areas under the actual conditions of use if the manufacturing situation as long as there would be no impact on the production environment or product quality. Other areas used for the qualification study shall have the lighting and light levels representative of the manufacturing or inspection areas where the VI is performed.

5.4.4 Light levels should be determined for the areas of operation and the area where the qualification is performed to confirm they are equivalent using a light meter capable of measuring between 200 to 1400 lux.

5.4.5 The use of ultraviolet (UV) light in the qualification studies to enhance the visibility of residues may be of benefit as many compounds fluoresce under UV light and this should be explored where possible. If UV is used in the qualification study it must become part of the inspection procedure.

5.5 *Selection of Surfaces for the Qualification Study:*

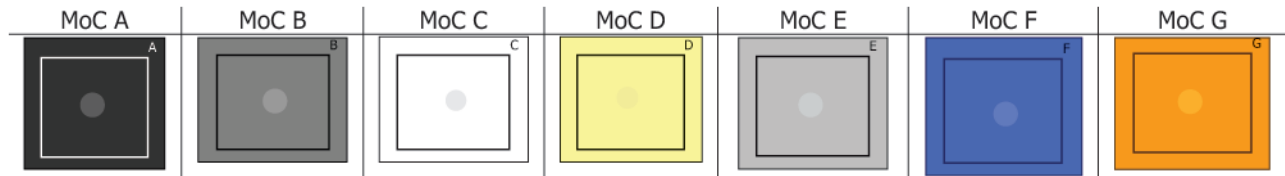
5.5.1 Surfaces used for qualification studies should be actual equipment or devices or where this is not possible surrogates representative of the actual equipment or devices may be used. There are equipment or devices that are not appropriate for visual inspection based on their design. Also where the condition of equipment in use for production may affect the visual detection of residues (e.g., stains, scratches) either the surrogate should be of an equivalent quality or that piece of equipment should be repaired or replaced. In general, such equipment may not be appropriate for visual inspection.

5.5.2 Spiking studies can be used to screen materials of construction for the “hardest-to-see surfaces” to narrow-down-determine the appropriate number of qualifications of operators/inspectors that need to be performed-performed where multiple compound/products/devices are being manufactured on common equipment. This section provides an example of an approach that can be used to select surfaces. Other robust approaches may be acceptable if justified.

5.5.2.1 A solution of a compound/product/residue is spiked onto multiple surrogate surfaces (for example, different materials of construction), which are then put in order by multiple experienced inspectors from the “hardest-to-see surfaces” to the “easiest-to-see surfaces.” The spiked surrogate surface that has the highest probability of being the “hardest-to-see surface” is then chosen for the qualification of VI studies. Any compound can be used for this study (see [Fig. 3 Appendix X1](#) and [Table 1](#) for an example).

5.5.2.2 If no one surrogate surface has a higher probability than the other surrogate surfaces, then any surrogate surface may be chosen for the qualification of VI studies, and in these cases, the most common surrogate surface may be chosen-chosen (e.g., 316L Stainless Steel with a #4 Finish).

5.5.2.3 When there are many different materials of construction because of minor parts (for example, gasket materials and so



NOTE 1—The solid blue line is predicted probability of detection and the brown dashed line is lower 95 % confidence bounds for the predicted probabilities. In this example, VRL represents the residue concentration at the lower 95 % confidence for 90 % probability of detection. Coupons of seven (7) different MoCs are spiked with a compound/product. Coupons are presented to inspectors in a random order and the inspectors rank them from “easiest to see” (1) to “hardest-to-see” (7).

FIG. X4.13 Analysis of Inspection Data in Selection of Hardest-to-See Material of Table X4.2 Construction

TABLE 1 Inspector Rankings of MoCs for the Difficulty of Seeing Residues (Ranking: 7 = Hardest / 1 = Easiest)

NOTE 1—In this example, nine out of ten inspectors scored Coupon C (probability = 0.9) and only one out of ten inspectors scored Coupon D (probability = 0.1) as the hardest-to-see of the seven coupon MoCs. None of the other coupons were ranked as the hardest-to-see (probability = 0.0). The residue on Coupon C is, therefore, selected for the VRL determination as the hardest-to-see MoC.

MoC	Insp 1	Insp 2	Insp 3	Insp 4	Insp 5	Insp 6	Insp 7	Insp 8	Insp 9	Insp 10	Rank	Prob
A	5	6	6	5	6	6	6	5	6	6	6	0.0
B	2	2	2	2	2	1	2	2	2	2	2	0.0
C	1	1	1	1	1	2	1	1	1	1	1	0.0
D	7	7	7	6	7	7	7	7	7	7	7	0.9
E	6	5	5	7	5	5	5	6	5	5	5	0.1
F	4	3	3	4	3	3	3	3	3	3	3	0.0
G	5	4	4	3	4	4	4	4	4	4	4	0.0

forth), these may be eliminated from these studies if a risk assessment shows that their surfaces do not pose a significant risk for VI and demonstrates that they do not make a significant contribution to residue levels in a batch. Materials contacting unit doses may not be suitable for such an exception.

5.5.2.4 Materials of construction with known surface properties in which the contrast between the surfaces and the residues make them easy to see (for example, stainless steel with a mirror finish, borosilicate glass) (e.g., during screening studies) may also be excluded from these studies if documented in the risk assessment.

5.5.2.5 Materials of construction with known surface properties in which the contrast between the surfaces and the residues make them difficult to see (for example, a white residue on a white matte surface) may not be appropriate for qualification studies of VI. In these circumstances reliance on visual inspection as the sole means of determining cleanliness may not be appropriate.

5.5.2.6 The selection of “hardest-to-see surface” surface(s) may be performed before the selection of the “hardest-to-see compound/product” compound(s)/product(s) depending on the risk assessment.

5.6 Selection of Products for the Qualification Study:

5.6.1 Spiking and visual ranging studies can be used to screen compounds/products/residues for the “hardest-to-see compound/products” compounds/products” to narrow down determine the appropriate number of qualifications of operators/inspectors that need to be performed.

5.6.1.1 For low HBEL products where their MSSRs are also low, there should also be a sufficient margin of safety to allow their exclusion from qualification studies otherwise these compounds would still require qualification studies. Where multiple low HBEL products are not visibly different from each other and the data from visual ranging studies indicate that their VRLs are likely to be near their MSSRs then these products should have the appropriate number of qualification studies performed based on the sound risk management and knowledge management.

5.6.2 Solutions of the compounds/products/residues at the same concentration are spiked onto the “hardest-to-see surface” surrogate surfaces/devices, which surfaces/devices and presented to the inspectors in a random order. The surrogate surfaces are then put in order by multiple experienced trained inspectors from the “hardest-to-see compounds/products” compound(s)/

product(s)” to the “easiest-to-see compounds/products.” compound(s)/product(s)” and ranked as a part of the ongoing qualification program. The spiked surrogate surface/device surface(s)/device(s) that has the highest probability of being the “hardest-to-see compounds/product” compound(s)/product(s)” is then chosen for the qualification of VI studies (see (Fig. 4 Appendix X2 and Table 2 for an example).

5.6.3 If no one compound/product/residue has a higher probability than the other compounds/products/residues, then any compounds/products/residues may be chosen for the qualification of VI studies.

5.6.4 The selection of “hardest-to-see compounds/product” compound(s)/product(s)” may be performed before the selection of “hardest-to-see surface” surface(s)” depending on the risk assessment.

5.7 Preparation of Surrogate Surfaces or Devices:

5.7.1 Surrogate surfaces (for example, coupons, devices) shall be prepared from the same materials of construction with similar finishes, coatings, and so forth as the equipment or device surfaces the VI qualification is being performed on (Practice G121). The type of surface finish or coating or both shall be identified by the user company of the equipment/device.

5.7.2 Surrogate surfaces shall be thoroughly cleaned and examined before preparation to ensure the surrogate surfaces are free from any defects (stains, scratches, and so forth) that may affect the qualification results. Surrogate surfaces with known defects should be removed from the set. representative of the worst case for the manufacturing equipment or device surfaces and relevant for the qualification.

5.7.3 Clean gloves should be worn when handling surrogate surfaces to protect from contamination from fingerprints.

5.7.4 For VI qualification studies to be valid, the surrogate surfaces shall be prepared in a manner that leaves residues a consistent level of the target residue ($\mu\text{g}/\text{cm}^2$) on the surrogate surfaces that are as close as surfaces. The actual level of $\mu\text{g}/\text{cm}^2$ possible in appearance to the residues that will be encountered in the manufacturing area of residue on the surrogate surface should be determined.

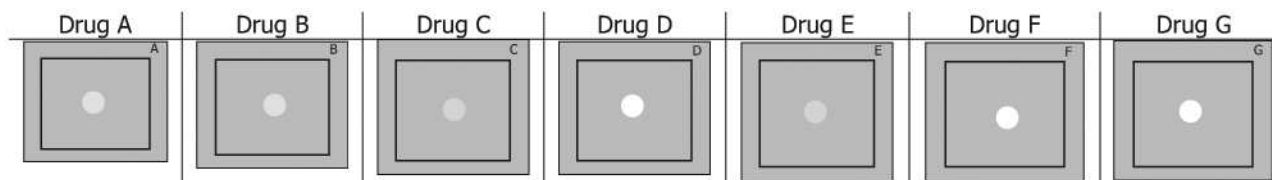
5.7.5 Surrogate surfaces should be prepared in a manner that simulates the conditions the residues will encounter after cleaning. For example, residues may have obvious edges or appear as a continuous layer which can affect the determination of the Visual Residue Limit. The effects of cleaning agents, drying conditions, etc. and historical information on residues should be understood and considered.

5.7.6 Ensure there is a balanced mix of clean and dirty/soiled surrogate surfaces.

5.7.6.1 Use a random number generator to select one half of the surrogate surfaces for use as standards for clean surfaces and the remaining surrogate surfaces for use as standards for dirty or soiled surfaces.

5.7.7 Surrogate surfaces—The dirty/soiled coupons or devices of the Material of Construction determined from 5.5 should be spiked and dried in a manner that simulates the actual conditions in the facility’s manufacturing area. For example, an API is dissolved in purified water, spiked onto the surrogate surface, and then dried in an oven at 90°C. This procedure would simulate the actual conditions in an operation involving a final purified water rinse on hot equipment surfaces in which API residue may dry quickly on the equipment. If the equipment is manually cleaned at room temperature, then spiking should simulate this condition. For API manufacturers, deposition with the solvent (for example, methanol) that is with a solution of the product or residue determined from 5.6 used for cleaning would be appropriate and allowed to dry.

5.7.7.1 Preparation of Surrogate Surfaces Specific to Pharmaceutical Products—For example, an API is dissolved in purified



NOTE 1—Coupons of the hardest-to-see MoC are spiked with the different compounds/products and then ranked from "easiest to see" to "hardest-to-see" compound/product.

FIG. 4 Example for Selection of Hardest-to-See Residues

TABLE 2 Inspector Rankings of Drugs for the Difficulty of Seeing Residues (Ranking: 7 = Hardest / 1 = Easiest)

NOTE 1—In this example, 5 out of 10 inspectors scored Coupon C (probability = 0.5) and 5 out of 10 inspectors scored Coupon E (probability = 0.5) as the hardest-to-see of the seven drugs. None of the other drugs were ranked as the hardest-to-see (probability = 0.0). As the results were equivocal, the residues of both Drug C and Drug E were both selected for the VRL determination as the hardest-to-see residues.

Drug	Insp 1	Insp 2	Insp 3	Insp 4	Insp 5	Insp 6	Insp 7	Insp 8	Insp 9	Insp 10	Rank	Prob
A	6	6	5	5	5	5	6	6	6	5	5	0.0
B	2	2	2	2	2	2	2	2	2	2	2	0.0
C	7	5	7	6	7	6	5	6	7	7	7	0.5
D	1	1	1	1	1	1	1	1	1	1	1	0.0
E	5	7	6	7	6	7	7	7	5	6	7	0.5
F	4	3	3	4	3	3	3	3	3	3	3	0.0
G	5	4	4	3	4	4	4	4	4	4	4	0.0

water, spiked onto the surrogate surface, and then dried in an oven at 90 °C. This procedure would simulate the actual conditions in an operation involving a final purified water rinse on hot equipment surfaces in which API residue may dry quickly on the equipment. If the equipment is manually cleaned at room temperature, then spiking should simulate this condition. For API manufacturers, deposition with the solvent (for example, methanol) that is used for cleaning would be appropriate. See Note 2.

NOTE 2—Evaporative drying has been studied for many solvents, including water, and there are significant differences in the deposition patterns of residues depending on the solvent (18). Consequently, the improper preparation of surrogate surfaces may lead to erroneous conclusions. The use of solvents (for example, methanol) to deposit the compounds that are cleaned under aqueous condition or drying them or both under conditions not encountered in operations (for example, under a nitrogen stream) are not recommended.

5.7.7.2 *Preparation of Surrogate Surfaces Specific to Medical Devices*—Medical devices are very diverse regarding materials, surface finish, design, construction and manufacturing processes. The surrogate surface shall be representative of the key features of the finished device for VI. Special consideration shall be given to (1) material composition; (2) surface finish based on manufacturing processes; and (3) design features such as back tapers or bore holes. Therefore, actual parts or three-dimensional surrogate parts are often used. Surrogate parts are typically used when actual parts are too expensive or not readily available for use.

(1) The process residue (e.g. a metal working fluid, a polishing abrasive, or a cleaning agent) shall be applied in well-defined amounts to the surrogate surface and the surface area covered by the applied process residue shall be determined in order to calculate the applied amount per surface area (µg/cm²). Dependent on the device design, it may be important to determine the VRL for several design features and/or on various surface finishes to establish the VRL for the device. Each selection of the various points mentioned above has to be justified in a risk assessment.

5.7.8 Surrogate surfaces shall be individually marked so inspectors may easily identify them during the qualification studies. If numbering is used to mark, random numbers should be assigned to minimize the likelihood that inspectors may remember prior evaluations.

5.7.9 Surrogate surfaces should be uniquely marked (such as labeled as to the material of construction, for example, 316L SS/#4 Finish or with the date of manufacture or both) to provide traceability, avoid mixups, mix-ups, and avoid invalidating the qualification studies.

5.7.10 After preparation, all surrogate surfaces should be examined to ensure they have been prepared correctly, including verifying that the blank surrogate surfaces do not have unintended stains, scratches, or fingerprints that may mislead the inspectors and invalidate the qualification study.

5.7.11 ~~Photographs~~ Digital images of the spiked surrogate surfaces after preparation and before use ~~should~~ shall be taken and stored for reference as a baseline condition of the surrogate surfaces for comparison and evaluation after a period of use. Such images should be representative of the appearance of the residue on the surface. Before performing a study, the surrogate surfaces should be examined. If a surrogate surface's appearance is significantly different from no longer representative in comparison to the original photographs, it ~~should be replaced~~ is not appropriate to use them in the study. Alternatively, standards may be used for reference.

5.7.11.1 It should be noted that digital data and the comparability of digital photography against physical specimens has