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 E55.14 on Measurement Systems and Analysis.

Current edition approved May 1, 2022. Published September 2022. Originally approved in 2020. Last previous edition approved in 2020 as E3263 – 20. DOI: 10.1520/E3263-22E01.

[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.

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.

3.2.3 *degradant, n*—product of the breakdown of a molecule through a degradation process.

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 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 $\mu g/cm^2$ 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) and is in accordance with FDA Process Validation Guidance Life Cycle approach.

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.

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 for Industry, PAT – A Framework 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

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

use" since 1979. In general, pharmaceutical manufacturers have been releasing some equipment and some compounds based on a "visual" inspection for many years and the industry 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 (**3**) 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/cm^2) (**4**). Another article claimed that residues can be seen down to 1 µg/cm^2 by using an additional light source (**5**). Another article claimed to see residues of several compounds down to approximately 0.4 µg/cm^2 (**6**). A series of studies found a range of 0.4 to >10 µg/cm^2 for several different compounds (**7**, **8**). Studies using a different spiking technique calculated detection limits for one residue at levels of 3, 5, and 7 µg/cm^2 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:*

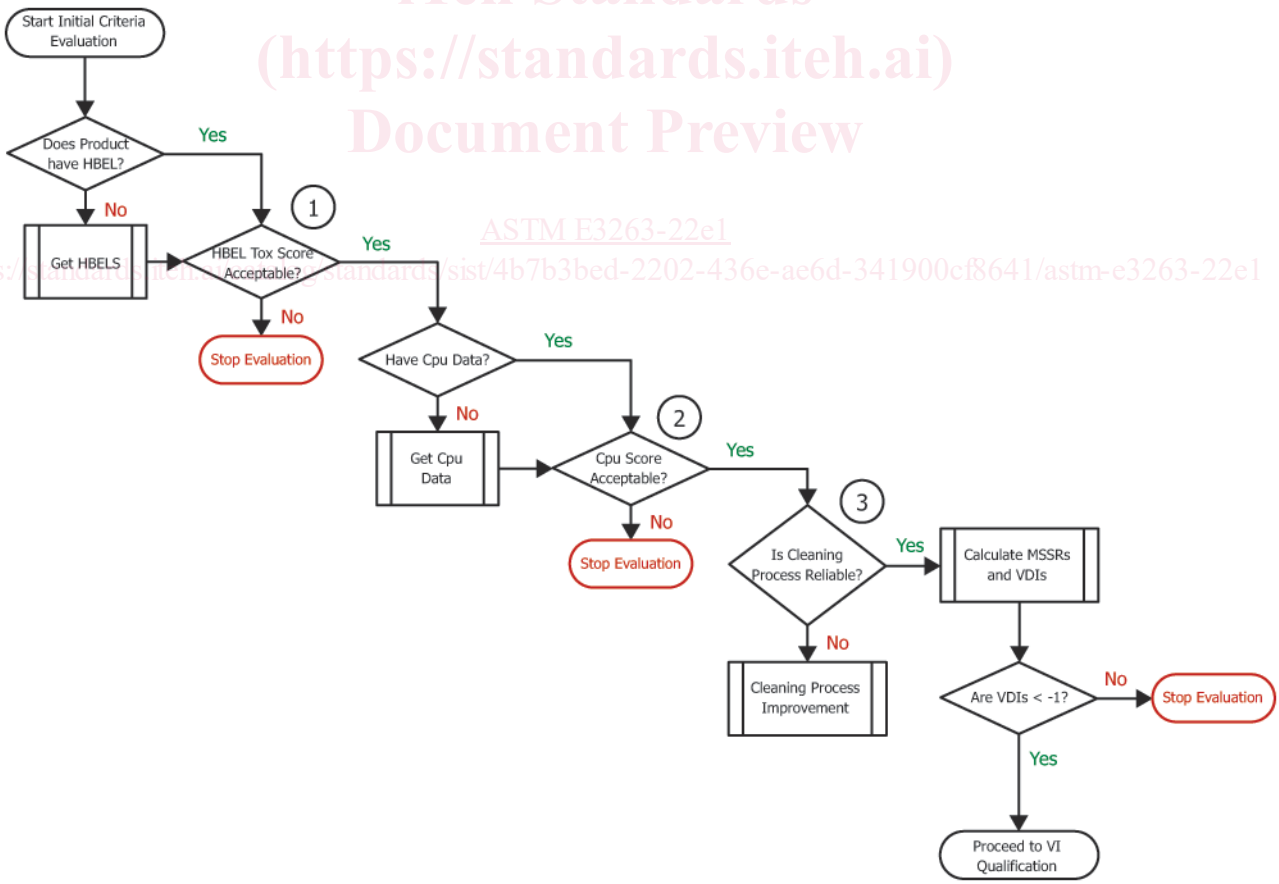
5.2.1 The following criteria for the release of equipment without analytical testing (after cleaning qualification is completed) are derived from EMA regulation/guidance and apply to the use of this practice (**2**). These same criteria are appropriate for qualifying VI for the validation of cleaning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

5.2.1.1 The compounds/products/residues selected for evaluation of VI shall have acceptable hazard levels based on their HBELs derived by a qualified expert. See 9.3.

5.2.1.2 The cleaning processes of the compounds/products/residues selected should be validated and not present any significant concerns for patient 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.



NOTE 1—① HBEL Toxicity Scores are calculated as in Reference (**12**). ② Cpu Scores are calculated as in Reference (**13**). Companies should determine what Toxicity Scores and Cpu Scores are acceptable in their organizations. ③ 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. 1 Example Flow Diagram for Initial Screening of Candidates for Visual Inspection

5.2.2 The design of the equipment/device has an impact on its inspection. Equipment/device design should be considered as one element of the 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 and the products selected for using VI only justified if the risk assessment provides a valid basis.

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.

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, µg/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 process residues identified as hazards (Guide E3106) should be determined.

5.3.4 The acceptability of residues for VI can be measured by using the Visual Detection Index (VDI) (**15**).

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:

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

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/cm^2 could be used. 10 µg/cm^2 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.

5.3.4.4 It should be understood that 10 µg/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 µg/cm^2, 1 µg/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).

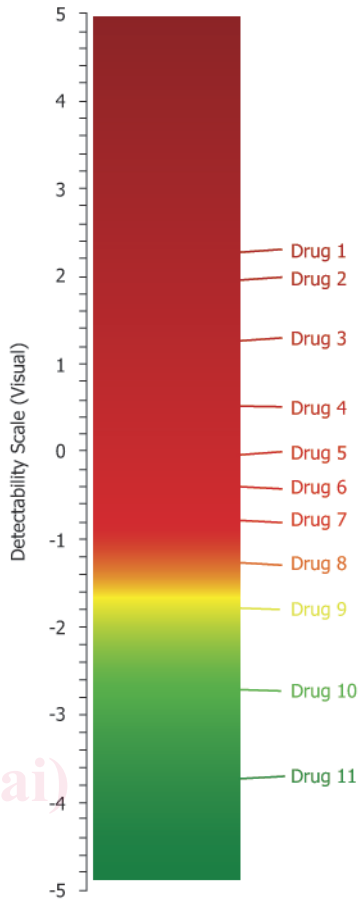
5.4.2.1 Examples of inspection conditions may be between light level of >X, viewing angles of between A and B, and distances of <Z.

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

Detectability Scales for :	Visual		
Substance Name	MSSR	VRL	Scale
Drug 1	0.05	10	2.301
Drug 2	0.1	10	2.000
Drug 3	0.5	10	1.301
Drug 4	3	10	0.523
Drug 5	10	10	0.000
Drug 6	25	10	-0.398
Drug 7	60	10	-0.778
Drug 8	180	10	-1.255
Drug 9	600	10	-1.778
Drug 10	5000	10	-2.699
Drug 11	50000	10	-3.699



NOTE 1—In this example, the MSSRs for eleven (11) drugs have been calculated based on their HBELs and compared to a VRL of 10 µg/cm^2. 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/cm^2) then more drugs may be candidates).

FIG. 2 Using the VDI as a Screening Tool for Candidates for Visual Inspection

be explored where possible. If UV is used in the qualification study it must become part of the inspection procedure.

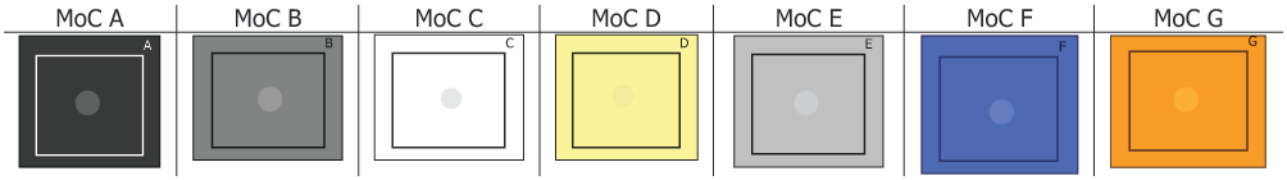
5.5 *Selection of Surfaces for the Qualification Study:*

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 determine the appropriate number of qualifications of operators/inspectors that need to be 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 (Fig. 3 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 (e.g., 316L Stainless Steel with a #4 Finish).



NOTE 1—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. 3 Selection of Hardest-to-See Material of 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 D (probability = 0.9) and only one out of ten inspectors scored Coupon E (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 D 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

5.5.2.3 When there are many different materials of construction because of minor parts (for example, gasket materials and so 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 (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(s)" may be performed before the selection of the "hardest-to-see 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 are used to screen compounds/products/residues for the "hardest-to-see compounds/products" to 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.

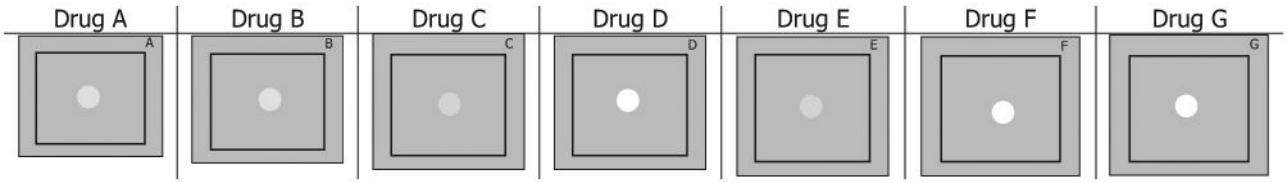
5.6.2 Solutions of the compounds/products/residues at the same concentration are spiked onto the "hardest-to-see surface" surrogate surfaces/devices and presented to the inspectors in a random order. The surrogate surfaces are then put in order by multiple trained inspectors from the "hardest-to-see compound(s)/product(s)" to the "easiest-to-see compound(s)/product(s)" and ranked as a part of the ongoing qualification program. The spiked surrogate surface(s)/device(s) that has the highest probability of being the "hardest-to-see compound(s)/product(s)" is then chosen for the qualification of VI studies (Fig. 4 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 compound(s)/product(s)" may be performed before the selection of "hardest-to-see 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



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

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 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 a consistent level of the target residue (µg/cm^2) on the surrogate surfaces. The actual level of µg/cm^2 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 The dirty/soiled coupons or devices of the Material of Construction determined from 5.5 should be spiked with a solution of the product or residue determined from 5.6 and allowed to dry.

5.7.7.1 *Preparation of Surrogate Surfaces Specific to Pharmaceutical Products*—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 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/cm^2). 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 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 Digital images of the spiked surrogate surfaces after preparation and before use 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 no longer representative in comparison to the original photographs, it 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 limitations due to various factors such as lighting type,

configuration, and overall level of lighting in the inspection area and the settings on the monitor used to display the image.

5.7.12 If one product is used as representative of a group of products in a qualification study, the residues of the other compounds/products shall be equivalent in appearance (for example, a white residue would not be equivalent to a blue residue).

5.8 *Surrogate Surface Storage and Handling:*

5.8.1 Surrogate surfaces can be easily damaged or contaminated and this could affect the results of the study so storage, handling, and maintenance of surrogate surfaces are important.

5.8.2 Clean gloves should be worn when handling surrogate surfaces to protect them from external contamination during handling.

5.8.3 When not in use, surrogate surfaces should be kept in a protective enclosure to protect from contamination or alteration of the clean or spiked surfaces during storage.

5.8.4 Surrogate surfaces should be examined before, and following, any qualification studies to ensure that they are free from any residues from extraneous sources (for example, dust, fingerprints, and so forth) that might interfere with the study and impact the qualification process.

6. Inspector Training

6.1 SOPs shall be written on how VI should be performed.

6.2 Inspectors performing VIs should be trained to ensure that an appropriate inspection is performed under appropriate conditions.

6.3 Inspectors need to demonstrate their ability to perform these inspections after training. Statistical techniques, such as measurement systems analysis, may be used to determine the effectiveness of the training. Proficiency of inspection can be demonstrated through attribute agreement analysis (Section 8).

6.4 Critical parameters and risks determined during the qualification of VI should be included in the SOP and training.

6.5 It is suggested that simulated residues should also be compared against appropriate controls for studying the ability of inspectors to differentiate between process residues and "false positives" such as those caused by watermarks, surface defects, or uneven surface finishing, and so forth, which are irrelevant for the inspection.

6.6 Inspectors should have eye exams on a defined schedule based on the level of risk. This requirement should be part of the risk assessment. ((**19**), USP Chapter <1790>).

6.7 If supplemental tools (such as boroscopes, UV lights, and so forth) for performing VI are used, inspectors shall be trained on their use.

7. Determination of Visual Residue Limits

7.1 This section describes statistically valid methods for determining the lowest spiked residue level for establishing Visible Residues Limits (VRLs).

7.1.1 The minimal visible amount of a residue is established through an endpoint dilution. Serial dilutions (suggested 1:5 dilutions) are prepared and a fixed volume of each dilution (e.g., 1 mL) is spiked on individual surrogates and allowed to dry.

7.2 This method is performed on the selected surrogate surfaces or devices spiked with known amounts of the selected compounds/products/residues spiked at a number of concentrations approximately in the expected range of the VRL. Trained inspectors examine the surfaces under controlled viewing conditions (for example, light, viewing angle, and viewing distance) for the presence of residue. The lowest level of residue that is detected by all inspectors is then considered the VRL for that particular product/compound residue (EN-12464).

7.3 *Statistically Derived VRLs:*

7.3.1 The objective of this VRL determination is to derive the lowest residue level that can be seen by all trained inspectors for the product/compound using statistical analysis of the spiked coupon study.

7.3.1.1 The approach described in 7.2 results in a rough approximation of the VRL and may set the VRL significantly higher than it should be and may not be statistically valid if the numbers of inspectors are too low (**10**).

7.3.2 The visual residue data collected during VRL determinations are binary (clean/dirty, yes/no) and the most suitable statistical technique that can be applied to binary data is binary regression, for example, using logistic or probit models. A logistic-regression-based approach has been proposed for VRL determination in the literature (**10**).

7.3.2.1 These techniques involve fitting a relationship between the binary response and explanatory variables such as spiked concentration, viewing distance, viewing angle, and light intensity. For modelling, a link function (for example, logit or probit) that transforms the expected values of the response variable to values that can be modeled using linear regression is used. See Note 3.

NOTE 3—Because of this generalization of linear models, these models are referred to as generalized linear models.

7.3.2.2 The regression parameters for the fitted model are estimated using maximum likelihood method. See Note 4.

NOTE 4—Maximum likelihood estimation is a technique used for estimating the parameters of a statistical model. In this technique, the model parameters (namely, maximum likelihood estimates) are obtained by maximizing the likelihood or log-likelihood functions (see equations). The parameter estimates are computed iteratively using algorithms such as Newton-Raphson or Fisher-scoring. For simple logistic regression, the likelihood function is given by:

$$L(\beta_0, \beta_1) = \prod_{i=1}^{n} p(x_i)^{y_i}[1 - p(x_i)]^{1-y_i}$$

and the log-likelihood is given by:

$$LL(\beta_0, \beta_1) = \prod_{i=1}^{n} [y_i \log (p(x_i)) + (1 - y_i)\log(1 - p(x_i))]$$

where:

x_1–x_n, and y_1–y_n = values of independent variable and binary response variable, respectively,
n = number of observations,
β_1 = intercept,
β_0 = slope parameter, and

$$p(x_i) = \frac{e^{\beta_0+\beta_1 x_i}}{1+e^{\beta_0+\beta_1 x_i}}$$

7.3.3 To determine the VRL through regression modeling, studies are performed on the selected surrogate surfaces or devices spiked with known amounts of the selected compounds/products/residues at concentrations spiked at multiple levels across the expected visible range. Trained inspectors examine the surfaces for the presence of residue on surrogate surfaces presented in a randomized manner under typical manufacturing viewing conditions (for example, lighting on the manufacturing floor, typical inspection procedures).

7.3.3.1 A spiked range comprising at least five concentrations (excluding zero or blank) is recommended for model fitting and statistical determination of VRL.

7.3.4 The inspectors record whether they can see the residue or not and the proportion of inspectors that report seeing the residue at each level is calculated.

7.3.5 The observed proportion of detection for each spiking level is the ratio of observers that detected the residue to the total number of observers. Fig. 5 shows an example of these observed proportions. It shows that the proportion of detection increases with the spiked residue concentration. The relationship is nonlinear, however, and the proportion of detection changes little at the high extreme of spiked residue. This pattern is typical because proportions cannot lie outside the range of 0 to 1.

7.3.6 For VRL determination, the proportion of detection is used as the dependent/response variable. (See Note 5.) The data are then fitted using a regression model and a link function to estimate probability of detection for different concentration levels. An example of a fitted relationship using logit link function is shown in Fig. 6.

NOTE 5—Modelling using statistical software does not require these intermediate proportions to be estimated. For fitting models using software, response variable can either be a binary variable encoded as 0 (for no detection) and 1 (for detection) or be specified in events/trials format (in which "events" is the number of inspectors that detected the residue and "trials" is the number of inspectors).

7.3.7 Based on the modeled relationship, lower 95 % confidence bounds for the fitted probabilities of detection are then estimated (see Appendix X1 for an example).

7.3.7.1 The number of inspectors and concentration range used for study can affect the width of the estimated confidence bounds. The number of inspectors and the sample size used for VRL determination should be justified in the risk assessment where the VRL is close to the MSSR and the risk is high. In such cases, more inspectors will be needed.

7.3.7.2 VRL is defined as the residue concentration that can be detected by statistically defined tolerances.

7.3.8 These analyses should be performed or reviewed by a qualified statistician and Quality Assurance.

7.3.9 Other strategies to model inspection data and determine VRL can be used if justified.

8. Qualification of Inspectors Using Attribute Agreement Analysis

8.1 All personnel who are involved in the release of equipment/devices by VI shall be qualified in this practice.

8.1.1 VI is considered qualified when all personnel have correctly identify all the spiked ("dirty") surrogate surfaces at the VRL.

8.1.2 VI, in which equipment or devices are being evaluated and approved for release or sale, is a type of analytical method. All analytical methods should be evaluated to determine their capability and suitability for the analysis they are being used for. Measurement systems analysis (MSA) can be used to assess a measurement system using a designed experiment to determine the suitability of the measurement system and identify any components of variation in the system (Guide E2782).

8.1.3 MSA, also known as gauge repeatability and reproducibility studies (gauge R&R), can evaluate:

8.1.3.1 The measuring device,

8.1.3.2 The procedures and operators,

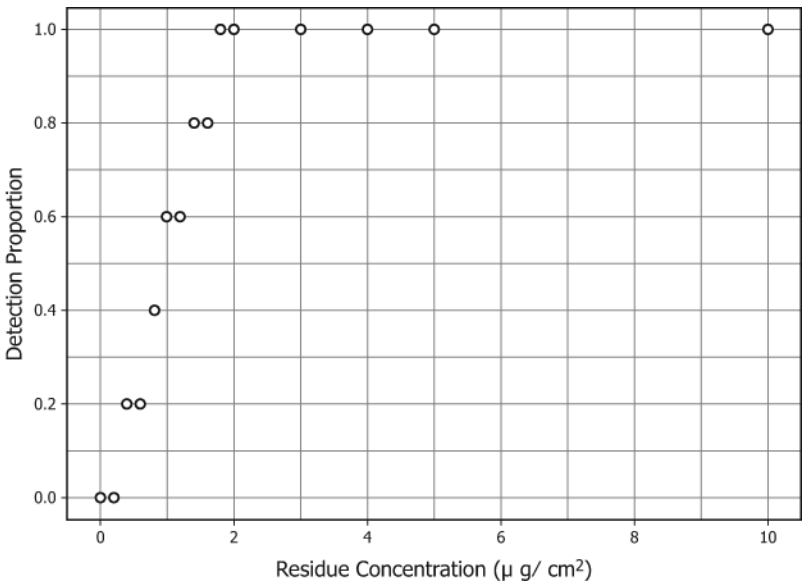
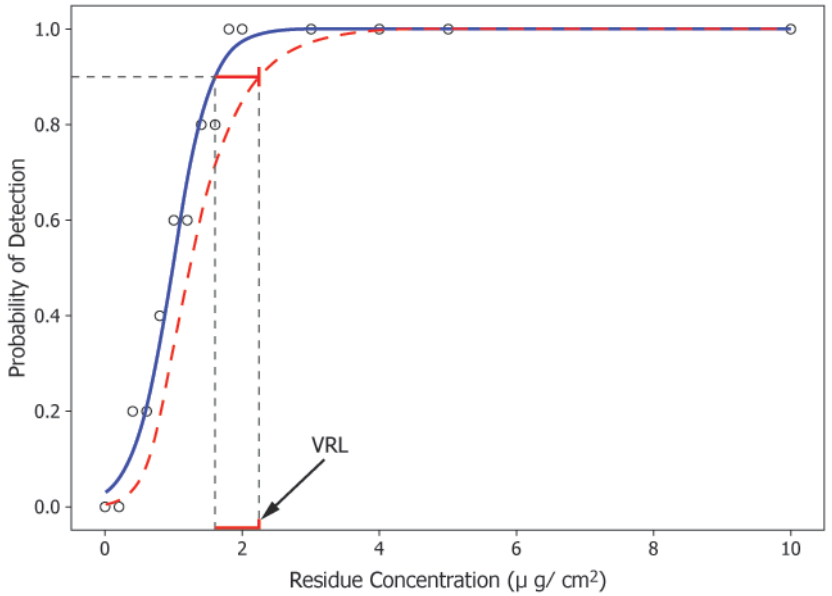


FIG. 5 Example Plot of Proportion of Detection against the Residue Level (μg/cm²)



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.

FIG. 6 Analysis of Inspection Data from Ref (10)

8.1.3.3 Any measurement interactions, and

8.1.3.4 The measurement uncertainty of individual measurement devices or measurement systems or both.

8.1.4 There are two types of gauge R&R: continuous gauge R&R and attribute gauge R&R that are used for continuous data and attribute data, respectively. Attribute agreement analysis evaluates the agreement of subjective data by multiple appraisers to determine how likely the appraisers are to misclassify an item they are inspecting. As VI is routinely used as a pass/fail methodology (that is, clean/dirty or soiled) this makes these results attribute data.

8.2 Qualification studies must be performed in a manner that is free from any sources of bias and efficiently collects the required information.

8.2.1 Prepare a statistically valid number of manufacturing, device or representative surfaces where actual surfaces are not readily available as described in 5.7 (**20, 21**).

8.2.2 Prepare data sheets for inspectors to record their observations including any metadata required by the study (e.g., name, department, shift).

8.2.2.1 There are statistical packages that can generate the necessary data sheets automatically.

8.2.2.2 Additional metadata can be added to the sheets for additional analysis (e.g., age, sex, years of service, wears glasses, etc.)

8.2.3 Arrange the surrogate surfaces in a randomized order on a table, cart, or another type of platform that allows for examination by the inspectors being qualified in an area determined from 5.7.2.

8.2.3.1 The surrogate surfaces can be placed one after another, side by side, allowing enough space between the surrogate surfaces to allow for examination by the inspectors without interference from other surrogate surfaces.

8.2.4 Perform a minimum of three trials for each inspector to account for day-to-day variability (**20, 21**). Attribute agreement analysis requires multiple trials so the qualification study be run at least three times to account for possible changes in consistency of inspection on the part of the inspectors.

8.2.4.1 The order of the surrogate surfaces must be randomized before each inspection.

8.2.4.2 It is recommended the study be run double-blinded in which the inspectors and the person executing the study do not know the actual preparation of the surrogate surfaces.

8.2.5 The inspectors shall record the results of each inspection including their name, the trial number, the identification of the surrogate surface being inspected, and the result of the inspection (clean/dirty).

8.2.6 Analyze the inspection results from the collected forms using Attribute Agreement Analysis.

8.2.6.1 The accuracy and misclassification rates of the data collected are calculated for each inspector, each trial, and each surrogate surface and across all trials (see Appendix X2 for calculations).

(1) There are several statistical packages that can perform attribute agreement analysis making these studies easy to perform and analyze so the use of a statistical software package is recommended. These statistical packages can also generate the necessary forms for the inspection.

(2) These statistical packages can present the calculated results in graphical format. These reports are typically a summary report, an accuracy report, and a misclassification report such as those generated using a statistical package (see Figs. 7-12 for examples).

8.2.7 These analyses should be performed by, or reviewed by a qualified statistician and the Quality Unit.