Risk-Management Assessment of Visible-Residue Limits in Cleaning Validation

A risk-management assessment of visible-residue limits (VRL) in cleaning validation of pharmaceutical formulations was conducted for both pharmaceutical pilot plant and manufacturing facilities. The authors discuss how potential risks were identified, analyzed for probability, considered for seriousness, and controlled through avoidance or mitigation. These opportunities for VRL implementation then were identified for both pilot plant and manufacturing settings.

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Before formal cleaning validation programs were instituted, visual inspection was the primary means of determining equipment cleanliness. The use of visual inspection is still typically a component of a cleaning validation program and for routine inspections of cleaning effectiveness, but the use of visual inspection as a sole criterion for equipment cleanliness has not been successfully implemented as a valid approach for cleaning validation.

A validated cleaning program based on quantitative visual inspections in conjunction with swab testing is possible. Acceptable visible-residue limits (VRLs) can be established in conjunction with and compared with swab results. Assuming the swab results demonstrated a validated cleaning procedure, if the results are in agreement, then the VRLs may be used going forward. A similar argument has been successfully used to defend the use of rinse sampling established in conjunction with swab results.

Mendenhall proposed the use of only visual examination to determine equipment cleanliness in 1989 (1). He concluded that visible cleanliness criteria were more rigid than quantitative calculations and clearly adequate. LeBlanc also explored the role of visual examination as the sole acceptance criterion for cleaning validation (2). Nonetheless, the US Food and Drug Administration saw the use of a visually clean criterion limited to between lots of the same product (3). Recent work described the implementation of VRLs for the introduction of new compounds into a pharmaceutical pilot plant with previously validated cleaning procedures (4, 5). VRLs were established for all new compounds and compared with the acceptable-residual limit (ARL). If the VRL was lower, then visual cleanliness was used to determine if the compound was a new worst-case requiring validation. Additional work established VRLs and acceptable viewing parameters for several marketed formulations under the more challenging viewing conditions associated with larger size manufacturing equipment (6). This work was conducted in an effort to determine if VRLs and visual inspection only could be adopted as an adequate methodology in a multiproduct pharmaceutical manufacturing

plant with previously validated cleaning procedures.

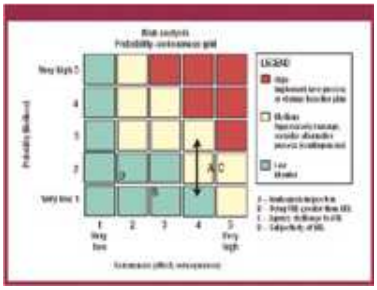

Figure 1: A risk-analysis grid using visual-residue limits (VRLs) and acceptable-residue limits (ARLs) as criteria.

The advantages of a properly validated and maintained VRL program are numerous. Visual inspection tests all visible equipment surfaces. Other than piping or tubing, most manufacturing equipment can be broken down such that the vast majority of surfaces are visible. For complex equipment and modules that are inaccessible to swabbing, rinse-sample testing can supplement visual inspections. VRL inspections reduce the personnel time needed to swab the manufacturing equipment. They eliminate ongoing analytical resource needs beyond the initial validation. Method development and validation resources for new development compounds are not required, which can be considerable. With the expanded use of VRL data in lieu of surface testing, the extent of testing and documentation necessary for each assessment is reduced, as well as the costs for long-term storage of the documentation and data. The advantage for the manufacturing area is the instant availability of visual-testing results, which minimizes equipment downtime while waiting for analytical results and increases manufacturing productivity. Savings in manpower, analytical instrumentation, and documentation free these resources for other tasks.

Table I: Applications and risk assessment of visible-residue limits (VRLs).

Implementing a VRL program includes the assumption of some degree of risk. Risks arise from the uncertainties of implementing a new cleaning strategy and can be diminished by generating more data, spending more resources, and taking more time. A balance of quality, time, and cost is necessary to manage risks associated with a VRL program. *Risk management* identifies the risks, analyzes the seriousness and probability of the risks, and plans appropriate responses to prevent or mitigate the risks. *Risk analysis* includes the benefits of viewing risk objectively and realistically, prioritizing resources, and justifying decisions to support prudent risk-taking

A risk-management assessment of VRL applications includes the identification of potential risks. The potential risk analysis determined the probability of occurrence and seriousness. Probabilities occur in low, medium, and high categories. Likewise, risk seriousness has designations of low, medium, and high. Individual risks populate a matrix of probability *versus* seriousness.

Risk evaluation leads to risk management. *Risk avoidanc*e takes the necessary steps to prevent a risk from occurring. *Risk mitigation* lessens the probability and seriousness of the risk. *Risk acceptance* is appropriate if the probability of occurrence is low or will not be serious enough to compromise product quality.

Risk identification

The most serious risk using VRLs is the potential that dirty equipment passes visual inspection and the subsequently manufactured formulation is compromised. Another risk is a regulatory agency challenge to the VRL approach. Finally, the subjectivity of visual assessment is a risk. The closer a VRL is to the ARL, the greater this risk becomes.

Risk analysis: key terminology

In addition to these risks, there are limitations when applying VRLs. To date, VRL determinations have been limited to stainless steel surfaces, which comprise the vast majority of equipment surfaces. Other materials of construction were not evaluated because of their poor reflective properties and would have to be addressed separately. VRL applications also have obvious limitations with respect to assessing microbiological control, particularly with wet-processing equipment. A cleaning-validation program would still need to assess the risks for microbial contamination of equipment. Surface sampling and rinse testing would be required to demonstrate a satisfactory state of control with respect to bioburden.

Risk analysis

Several causes are possible for dirty equipment passing visual inspection and compromising the subsequently manufactured formulation. The most likely scenario is that the inspector either did not perform a 100% inspection or performed an inadequate inspection on the equipment. As shown in Figure 1, the seriousness of an inadequate inspection is high because the subsequent batch could be compromised. The range of probability of an inadequate inspection depends on several factors. Training of the inspectors is a crucial component if VRLs are used to determine equipment cleanliness. Each active pharmaceutical ingredient (API) has a characteristic VRL, and inspectors must be familiar with the appearance of each residue. Visual inspection must be performed appropriately by inspecting all contact surfaces of the product with proper viewing angles of lighting and equipment. Documented training must be updated as new APIs and formulations are introduced into the manufacturing matrix.

VRLs resulting in residues above the ARL are a potential risk. A comparison of the VRL relative to the ARL is essential before any use of VRLs is initiated. The VRL must be lower than the ARL to use the VRL for cleaning evaluation. Although the seriousness for this risk is high, the probability is low.

The risk of a regulatory agency challenge is more likely when using VRLs only if there is not an initial validation study incorporating surface or rinsate testing. FDA has stated that the use of visual examination is limited between batches of the same product (2). Agencies from the European Union, Japan, and Canada also are likely to challenge a cleaning validation program using VRLs. The probability of an agency questioning the use of VRLs is high. The seriousness of the risk depends on the extent of VRL use and the data generated to support VRL use. VRL implementation can range from very specific situations, to more general applications, to the basis for an entire cleaning validation program. The data to support the use of VRL can range from a single, general limit (7, 8) to specific VRL determinations for each API and drug product (4, 6).

The subjectivity of VRL determinations and routine visual inspections are an ongoing risk. The probability and seriousness of this risk depend on the extent of training, ongoing monitoring, and VRL data generation, which can be minimized in a well-run VRL program by using at least four observers to determine VRLs and redundant monitoring, resulting in low probability and low seriousness.

Management of risks

Proper risk management can mitigate or eliminate the probability and seriousness for a given risk. Ideally, all risk would be eliminated, but in reality risk is reduced to an acceptable level. Universal visual inspection complemented by swab testing minimizes the probability of soiled equipment being used for subsequent manufacturing.

The risk minimization of using visual inspection and VRLs is ensured by a 100% inspection of the equipment surface that verifies product residue has been removed to an acceptable level. Inspector training should include familiarity with all manufacturing equipment, including disassembly, cleaning, and the appearance of visible residues for each API and product. The inclusion of new equipment, APIs, or products would necessitate additional training. A well-trained inspection group significantly decreases the risk of soiled equipment passing inspection.

Validated cleaning procedures should include specific instructions for disassembly and assembling equipment. Visual inspection and 100% access to all contact surfaces of the product will help mitigate the risks of undetected product carryover. Care must be taken to ensure that all contact surfaces of equipment products are inspected with appropriate lighting and viewing angles. For complex equipment, additional routine testing of rinse samples could be considered to supplement visual inspections.

Standard operating procedures for equipment cleaning also should address the issue of recleaning visibly soiled equipment. Once a visible soil is identified, a documented follow-up procedure ensures the equipment is recleaned and an investigation is conducted to determine the root cause of the issue and possible need to revise the cleaning procedure. With proper procedures in place, risk for a visual inspection is comparable to risk for other inspection methods.

The ARL should be determined before the VRL is established. The VRL is established experimentally and compared with the ARL. Only VRLs below the ARL level justify the use of visual inspections as a surrogate to surface sampling. Experimental VRL levels should be verified by at least four inspectors to minimize subjectivity. This procedure should minimize the risk of a VRL resulting in residues above the ARL.

A regulatory question on the use of VRLs should be anticipated. A sound justification of the extent of VRL used backed up by solid VRL data will mitigate potential agency concerns. To further mitigate regulatory risks, the initial validation of a new cleaning procedure may incorporate both surface sampling and visual inspection. Once cleaning performance has been validated with quantitative surface residual data and correlated to VRL data, the regulatory risks with extended use of VRL data would be reduced. VRL data were generated for specific APIs, excipients, and formulations (4, 6). Of the 39 marketed formulations evaluated to date for VRL, 27 formulation VRLs were <1 $\mu g/cm^2$; 10 VRLs were 1–2 $\mu g/cm^2$; 1 VRL was 2–3 $\mu g/cm^2$; and only 1 VRL was 3–

4 µg/cm^2 . The VRLs were generally well below a baseline ARL of 4 µg/cm^2 , further reducing the risk of carryover and mitigating potential regulatory concern.

Redundancy can add value to VRL determination and routine visual inspections with minimal additional resource requirements. Several personnel can check the equipment sequentially. Personnel cleaning the equipment, the inspector, and the subsequent formulator can all sign off that the equipment is clean. Two or more inspectors can perform the visual examination and document passing visual inspections. Other combinations of personnel are just as effective. In addition, the frequency of an ongoing monitoring program can be increased using visual inspections in place of swab testing.

Uses of VRLs by a pilot-plant facility

The use of VRLs has previously been described (4, 5) for the introduction of new compounds into a pilot plant. Before a new compound is manufactured in the pilot plant, a VRL is established for the API. After the initial batch is manufactured, the equipment is cleaned and visual inspection using the VRL confirms the current cleaning procedure is sufficient and that the new compound is not a new worst-case requiring further validation. This process has been successfully implemented without compromising product quality. This application, along with its risk mitigation, is shown in Table I.

VRLs also are used for periodic assessment of cleaning in the pilot plant. Monthly independent visual inspections using VRLs are conducted on several pieces of equipment to ensure that routine cleaning removes all product residues. These inspections are in addition to routine visual inspections for cleanliness conducted after each use by the manufacturing technician. Over the course of the year, these independent periodic inspections check all of the different types of equipment in the pilot plant to generate a comprehensive review of ongoing cleaning effectiveness in the pilot plant.

Other uses of VRL in the pilot plant include technology transfer to a contract or other manufacturing facility. Since cleaning procedures between facilities are different, VRLs would be a quick, simple verification of cleaning in place of analytical method transfer and testing. This strategy applies more to early development where the number of manufactured batches is limited and for compounds that are relatively nontoxic.

VRLs also can be used for the introduction of new equipment into the facility. VRLs would be used to ensure baseline cleanliness and demonstrate equivalency with respect to the cleaning efficacy of a previously validated procedure. Developing the cleaning procedure for new or modified equipment in with VRLs is an efficient way to get equipment on line.

The optimization of new cleaning procedures during development is a potential application for VRLs. Cleaning cycle times could be challenged with VRL determination as the acceptance criteria. A more immediate benefit would be realized with manual cleaning procedures. Personnel who clean the equipment could effectively determine optimal scrub times and rinse volumes with a visual limit.

The cleaning-validation program of the pilot plant was based on qualitative visual inspection and swab-sample testing (9). A recent cleaning validation study (10) used VRLs along with swab-sample testing. The cleaned equipment passed both the swab testing and VRL inspection. Nonetheless, the swab-assay results were higher than expected based on the VRL data. An investigation concluded that the compound had reacted and formed an enantiomer with greater ultraviolet absorbance. The investigation demonstrated the value of establishing VRL data in conjunction with swab recoveries.

Uses of VRLs in a manufacturing facility

Several opportunities to apply VRLs as a surrogate to surface sampling have been identified in manufacturing facilities using good manufacturing practices (GMPs). Process controls and procedures also have been identified to mitigate the risks when applying VRLs in a GMP facility. Given that VRL determinations for drug-product formulations have been established (4, 6) and the relative accessibility to visual inspections with this equipment, the scope of these applications would be primarily applicable to pharmaceutical manufacturing and primary packaging operations.

As with pilot-plant facilities, VRL data may be used to develop new or optimize existing cleaning procedures. For manual cleaning procedures where the VRL is less than the ARL, the extent of routine documentation and cleaning records could be streamlined in a GMP facility. Once optimal scrub times and rinse volumes have been validated and incorporated into the cleaning procedure, visual cleanliness may be the only critical cleaning parameter that would require documentation on a routine basis. With VRL data, a check by a second person for visual cleanliness confirms performance and ensures that the level of residuals is below the acceptable residue level. This procedure may obviate the need to record actual cleaning parameter data *(i.e.*, scrub times and rinse volumes) on a routine basis and reduce the volume of GMP documentation that must be maintained for marketed drug products.

VRL data and visual inspection may be applied to support the introduction of new products into existing validated product matrices. The use of product matrices or bracketing product residues to validate a "worst case" for multiproduct equipment modules is a common practice in industry and supported by regulatory guidance (2, 11–13). Best practices include an evaluation of the different products and intermediates with respect to solubility and cleanability. Laboratory studies may be performed to directly compare the relative cleanability between the targeted compounds and products. Methodologies for rapid and inexpensive testing for cleanability have previously been reported (14). The relative toxicity data for all compounds in the matrix should also be reviewed, with the ARL set using the most potent compound. To validate the matrix, validation studies would challenge the cleaning on the worst-case compound to remove using an ARL calculated for the most potent compound in the matrix. As new products are introduced, toxicity and cleanability must be assessed as to whether the compound represents a new worst case. If not a new worst case, the VRL of the new compound can be compared with the validated ARL. If the new compound is less than the ARL, visual inspection alone should be satisfactory for revalidation of the cleaning procedure for a new product.

The interval of use (manufacturing campaign) and the interval between end of use and cleaning are process parameters that must be validated. Theoretically, the more batches

a piece of equipment processes, the greater the soil load, and the more difficult it is to clean. Hence, the need to challenge cleaning cycles after campaigns of different lengths. Nonetheless, some products' physical, chemical, and surface adhesion properties do not change over the campaign length. For manufacturing these products (dry processing), certain types of equipment do not allow residues to accumulate over time by design. This equipment is sloped for gravity removal of product, whereby the soil load (both the amount and nature of the soil) after one batch is comparable to the load after multiple batches within a campaign (*i.e.,* "freely draining"). This can be verified by visual inspection on a routine basis. For stable products, manufactured in freely draining equipment, there should be low-to-no process risks with respect to extending a validated campaign length based on visual inspection. Routine inspections for visual cleanliness would mitigate any potential process risks with carryover of process residuals and confirm cleaning performance. This same rationale could be applied to extending validated times for the interval between the end of use and equipment cleaning.

Once a cleaning process is validated in a GMP manufacturing environment, the process should be monitored periodically to ensure consistent and robust performance. Independent visual inspections should be incorporated into the periodic assessment program to confirm that cleaning processes remain in a state of control. A second person should check for visual cleanliness, and the frequency of recleaning is an appropriate metric for assessing cleaning performance. This additional control helps to ensure robustness of the validated cleaning procedure. With an appropriate VRL program, visual inspection may be used rather than surface and rinsate testing to demonstrate continued consistent cleaning performance.

Conclusion

Visible-residue limits (VRL) have been evaluated for pilot plants and manufacturing facilities from a risk-assessment perspective. Opportunities for VRL implementation have been identified with the acceptable mitigation of the associated risks.

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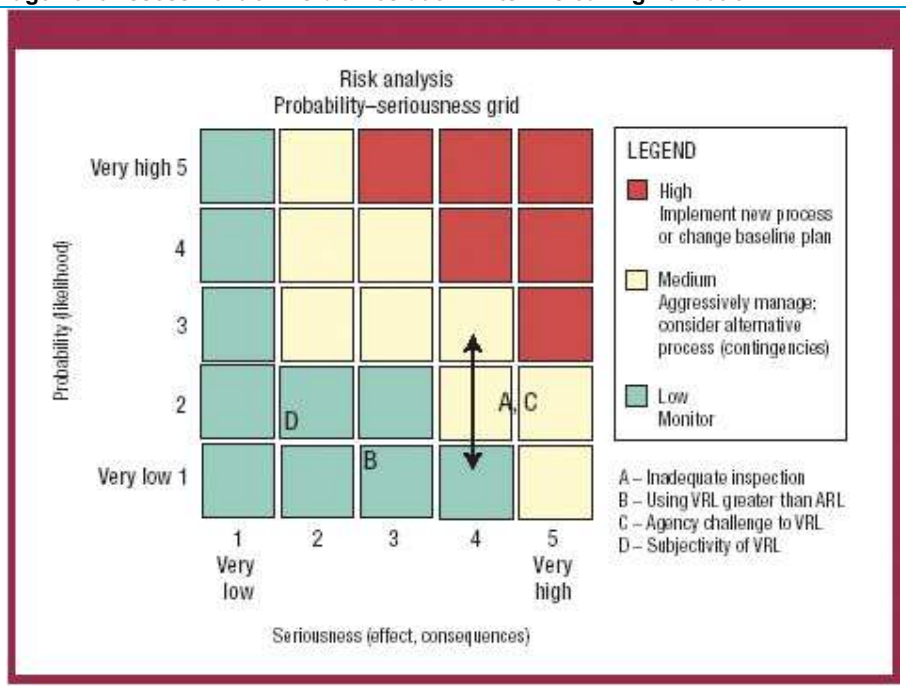

Figure 1: A risk-analysis grid using visual-residue limits (VRLs) and acceptable-residue limits (ARLs) as criteria.

Risk-Management Assessment of Visible-Residue Limits in Cleaning Validation

Table I: Applications and risk assessment of visible-residue limits (VRLs).

Application of visible-residue limits	Pilot plant and manufacturing	Process risk	Risk mitigation
New compound introduction	Pilot plant	Low (new worst case)	• VRL determination • Redundant inspection • Evaluate API's physical properties
New compound introduction	Manufacturing	Low (new worst case)	• Redundant inspection • Evaluate formulation's physical properties and cleanability
Periodic assessment	Pilot plant	Low (carryover)	• Redundant inspection • Periodic swab confirmation
Periodic assessment	Manufacturing	Low (carryover)	• Redundant inspection • Periodic assessments trending performance based on visual inspections
Technology transfer	Pilot plant	Low	• Redundant inspection
New equipment introduction	Pilot plant	Low (cleaning procedure does not work)	• Redundant inspection • Evaluate cleanability *versus* current equipment
Campaign-length extension	Manufacturing	Low to none	• Evaluate formulation's properties and equipment cleanability • Redundant inspection
Cleaning procedure optimization	Pilot plant	None	• Surface sampling after optimization
Cleaning procedure optimization	Manufacturing	None	• Surface sampling and validation after optimization
Reduced cleaning documentation (manual cleaning, equipment accessible to visual inspection	Manufacturing	Low to none	• Data to demonstrate VRL < ARL • All cleaning parameters demonstrated during validation

API is active pharmaceutical ingredient; ARL is acceptable-residue limit.

Table I: Applications and risk assessment of visible-residue limits (VRLs).

Risk-Management Assessment of Visible-Residue Limits in Cleaning Validation

Risk analysis: key terminology

Implementing a program for visible-residue limits includes the assumption of some degree of risk, and it is important to understand the basic terminology.

- *Risk acceptance* is appropriate if the probability of occurrence is low or will not be serious enough to compromise product quality.
- *Risk avoidance* takes the necessary steps to prevent a risk from occurring.
- *Risk evaluation* leads to risk management.
- *Risk management* identifies the risks, analyzes the seriousness and probability of the risks, and plans appropriate responses to prevent or mitigate the risk.
- *Risk mitigation* lessens the probability and seriousness of the risk.

Risk analysis: key terminology

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