Risk-Based Cleaning Validation in Pharmaceutical Manufacturing: A Comprehensive Review

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Article

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Abstract

Cleaning validation remains a cornerstone of pharmaceutical quality assurance, ensuring that manufacturing equipment is consistently cleaned to predetermined acceptance criteria that protect patient safety and product quality. The pharmaceutical industry has witnessed a significant paradigm shift from traditional compliance-based approaches toward science-based, risk-based methodologies for cleaning validation. This paper provides a comprehensive review of risk-based cleaning validation, examining the regulatory framework established by ICH Q9 and related guidelines, the evolution of acceptance criteria from arbitrary limits to health-based exposure limits, and the application of quality risk management tools such as Failure Mode and Effects Analysis. The lifecycle approach to cleaning validation, sampling methodologies, and strategies for preventing cross-contamination in multi-product facilities are discussed. This review synthesizes current literature and regulatory expectations to provide pharmaceutical professionals with practical guidance for implementing robust, scientifically justified cleaning validation programs.

Keywords: cleaning validation; risk-based approach; ICH Q9; health-based exposure limits; FMEA; cross-contamination; pharmaceutical manufacturing

1. Introduction

Cleaning validation in pharmaceutical manufacturing has evolved considerably over the past three decades, transitioning from a compliance-driven exercise to a scientifically rigorous, risk-based process that enhances both patient safety and manufacturing efficiency [1]. The fundamental objective of cleaning validation is to provide documented evidence that cleaning procedures reliably and reproducibly reduce residual contamination, including previous product residues, cleaning agent residues, and microbial contaminants to levels below acceptable safety limits [2].

The pharmaceutical industry historically approached cleaning validation primarily as a compliance exercise, with activities generally established based on regulatory expectations from inspections rather than on science-based master plans or risk assessments [3]. This reactive approach often resulted in inefficient resource allocation and validation programs that failed to address the actual risks associated with cross-contamination. The publication of ICH Q9 Quality Risk Management in 2005 marked a significant turning point, providing a framework for applying risk management principles to pharmaceutical operations, including cleaning validation [4].

Cross-contamination in multi-product pharmaceutical manufacturing facilities can significantly impact both product safety and quality [5]. Regulatory agencies worldwide now expect manufacturers to implement cleaning validation programs that not only meet good manufacturing practice standards but also integrate ongoing monitoring and continuous improvement through a risk-based approach [6]. This paper examines the current state of risk-based cleaning validation, exploring regulatory frameworks, methodological approaches, and practical implementation strategies.

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2. Regulatory Framework for Risk-Based Cleaning Validation

2.1. ICH Q9 Quality Risk Management

The International Council for Harmonisation's ICH Q9 guideline establishes two primary principles of quality risk management that directly apply to cleaning validation: the evaluation of risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient, and the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk [4]. Annex II of ICH Q9 specifically identifies cleaning validation as an area where quality risk management principles can be applied, including determining acceptable cleaning validation limits and identifying the scope and extent of verification activities [7].

The ICH Q9 quality risk management process consists of four primary components: risk assessment, risk control, risk communication, and risk review [4]. Risk assessment involves identifying hazards and analyzing and evaluating the risks associated with exposure to those hazards. Risk control focuses on decision-making to reduce and accept risks, with the amount of effort used for risk control proportional to the significance of the risk. These principles enable manufacturers to prioritize cleaning activities based on scientific risk rather than arbitrary procedures [8].

2.2. Health-Based Exposure Limits

The European Medicines Agency guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities represented a paradigm shift in how cleaning limits are established [9]. Health-based exposure limits, including Permitted Daily Exposure (PDE) and Acceptable Daily Exposure (ADE), are derived through structured scientific evaluation of all available pharmacological and toxicological data, including both non-clinical and clinical data [10].

The PDE represents a substance-specific dose that is unlikely to cause harm if an individual is exposed to it daily for a lifetime [11]. This approach is considered superior to previous methods for setting cleaning limits, such as using predetermined general limits like 10 ppm or fractions of the median lethal dose [5]. Research has demonstrated that for approximately 15 percent of pharmaceutical compounds studied, limits based on the traditional 1/1,000 dose criterion were not adequately protective, while for the remaining compounds, health-based limits provided more appropriate and scientifically justified acceptance criteria [12].

2.3. ASTM Standards

The American Society for Testing and Materials has published two significant standards that support risk-based cleaning validation: ASTM E3106 Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation, and ASTM E3219 Standard Guide for Derivation of Health-Based Exposure Limits [3]. These standards apply a lifecycle approach to cleaning validation, from development through validation to cleaning process verification, and can be applied to all dosage forms, active substances, and clinical supply production [13].

ASTM E3106 recommends that risk assessments for cleaning validation activities should consider acceptable daily exposure values, the threshold of toxicological concern concept, selection of analysis methods, and characterization of process residues including solubilities and adhesion behavior [13]. The standard emphasizes that the level of cleaning should be commensurate with the level of risk that the cleaning process poses in relation to the related production processes [14].

 doi:10.20944/preprints202511.2242.v1

3. Quality Risk Management Tools in Cleaning Validation

3.1. Failure Mode and Effects Analysis

Failure Mode and Effects Analysis (FMEA) represents one of the most widely used risk assessment tools in pharmaceutical cleaning validation [15]. FMEA is a systematic, step-by-step approach to identify and prioritize possible failures in a design, manufacturing, or assembly process [16]. The methodology examines individual components of a system to determine how each component could fail and the effect of that failure on system stability [17].

In FMEA, potential failure modes are assigned scores for severity, occurrence (probability), and detectability. The Risk Priority Number (RPN) is calculated by multiplying these three values, enabling prioritization of failure modes requiring immediate attention [18]. High RPN values indicate that the failure mode can result in significant negative effects, has a high likelihood of occurring, and has insufficient controls to detect it before affecting the customer [19]. Organizations typically use RPN thresholds between 40 and 150, depending on the development stage of their process [20].

For cleaning validation specifically, FMEA can be applied to identify potential failure modes in the cleaning process, evaluate their likely impact on product quality and patient safety, and prioritize control measures [21]. This includes assessment of equipment design factors, cleaning procedure parameters, personnel training, and analytical method performance [22].

3.2. Other Risk Assessment Methods

ICH Q9 identifies several additional risk management tools applicable to cleaning validation, including Failure Mode, Effects, and Criticality Analysis (FMECA), Fault Tree Analysis (FTA), Hazard Analysis and Critical Control Points (HACCP), Hazard Operability Analysis (HAZOP), and Preliminary Hazard Analysis (PHA) [4]. Risk ranking and filtering techniques can also be employed to evaluate and rank risks based on quantitative or semi-quantitative assessment [7].

The selection of appropriate risk assessment tools should be based on the specific application and the level of detail required. Simple processes may require only qualitative risk assessment, while complex multi-product facilities may benefit from more detailed quantitative analyses [23].

4. Establishing Acceptance Criteria

4.1. Maximum Allowable Carryover Calculations

The Maximum Allowable Carryover (MACO) represents the maximum residue from a previous product that can remain on shared manufacturing equipment without compromising subsequent products [24]. MACO calculations form the basis for establishing cleaning validation acceptance criteria and can be calculated using several approaches: health-based (ADE/PDE), therapeutic dose-based, toxicological (LD50-based), and fixed limits such as 10 ppm [25].

Current regulatory thinking strongly favors health-based limit calculations using ADE/PDE values, as these are calculated based on scientifically sound toxicological data and incorporate a risk-based approach [26]. The traditional approaches using fixed limits like 10 ppm or 0.001 of the minimum therapeutic dose are increasingly considered outdated and potentially either overly conservative for low-risk products or insufficiently protective for highly potent compounds [27].

Research comparing PDE-based limits with traditional approaches has demonstrated that health-based limits provide more appropriate risk management for the full spectrum of pharmaceutical compounds [12]. Patel and Patel [28] demonstrated the importance of empirical cleanability studies in worst-case product determination, showing that Carbidopa exhibited significantly lower removal efficiency compared to Levodopa across multiple cleaning methodologies, with residuals exceeding acceptance limits under water-only cleaning conditions.

 doi:10.20944/preprints202511.2242.v1

4.2. Visible Residue Limits

Visible Residue Limits (VRLs) represent the lowest level of residue that can be seen by trained observers under defined observation parameters [29]. VRLs have been established for numerous active pharmaceutical ingredients, excipients, and formulations, with typical detection levels ranging from less than 0.4 to greater than 10 μg/cm² depending on the compound and viewing conditions [30].

The relationship between VRL and the calculated Acceptable Residue Limit (ARL) is critical for determining the appropriate role of visual inspection in a cleaning validation program [31]. When the VRL is lower than the ARL, visual cleanliness can serve as the primary acceptance criterion, potentially streamlining routine documentation requirements [32]. Factors affecting VRL detection include observer viewing distance (optimally less than 10 feet), viewing angle (greater than 30°), ambient light level (greater than 200 lux), and residue composition [33].

5. Sampling Methods and Analytical Considerations

5.1. Swab Sampling

Direct surface sampling using swabs represents the preferred method for evaluating cleaning effectiveness, as it allows assessment of specific locations including hard-to-clean areas [34]. The procedure involves pre-wetting a swab with an appropriate solvent, systematically swabbing a defined surface area with overlapping patterns in vertical and horizontal directions, and extracting the swab for analysis [35].

Recovery studies are fundamental to cleaning validation, demonstrating the ability to consistently recover residues from equipment surfaces [36]. Regulatory guidelines from various agencies specify different thresholds for acceptable recovery: the Parenteral Drug Association considers 70% excellent and 50% acceptable, the World Health Organization considers values above 80% good and between 50-80% reasonable, and the Active Pharmaceutical Ingredients Committee recommends 90% for exceptional recoveries and 50% as minimum acceptable [36].

5.2. Rinse Sampling

Rinse sampling provides an indirect assessment of equipment cleanliness and is particularly useful for equipment with internal geometries where direct swab access is limited [37]. While regulatory guidance indicates a preference for direct sampling, both methods are clearly accepted when properly validated [38]. The choice between swab and rinse sampling depends on equipment accessibility, geometry of product-contact surfaces, and the ability to demonstrate quantitative recovery [39].

A critical consideration for rinse sampling is that residues must be soluble in the rinse solution and not physically occluded in equipment surfaces [34]. Recovery studies for rinse sampling should simulate actual rinsing conditions to demonstrate whether the process quantitatively removes surface residues [38].

5.3. Analytical Methods

Analytical methods for cleaning validation samples must be validated for their intended use, with the detection limit as the primary validation parameter for limit tests [40]. High-performance liquid chromatography (HPLC) methods typically provide sensitivity well below most calculated acceptance limits, though sensitivity depends on the chemical structure of the residue and detector capabilities [40].

Total Organic Carbon (TOC) analysis offers a non-specific alternative that measures organic carbon content without identifying the specific compound [41]. While non-specific methods may not distinguish between different residues, they provide rapid turnaround and can effectively monitor

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overall cleanliness levels. The use of TOC may be appropriate where indicated and justified, particularly for routine monitoring [10].

6. Lifecycle Approach to Cleaning Validation

6.1. Stage 1: Process Design

The cleaning validation lifecycle approach, aligned with FDA process validation guidance, consists of three stages: process design, performance qualification, and continued process verification [42]. Stage 1 involves cleaning agents and supplier selection, identification of critical parameters and cleaning methods, laboratory and pilot testing, utility considerations, process equipment design review, analytical test method validation, residue limit establishment, and visual inspection criteria development [43].

Laboratory-scale cleanability studies represent an efficient approach to developing initial cleaning process knowledge and understanding [44]. These studies can answer typical cleaning validation questions by measuring cleanability using gravimetric or analytical methods, following ASTM G121 Standard Practice for Preparation of Contaminated Test Coupons for the Evaluation of Cleaning Agents [44]. Cleanability data enable identification of worst-case products and support equipment grouping strategies [45].

6.2. Stage 2: Performance Qualification

Stage 2 serves as a readiness check to ensure the cleaning process can be validated, involving verification that suppliers have been approved, analytical methods validated, personnel trained, and process equipment qualified [42]. Validation studies should include a minimum of three successful runs demonstrating that cleaning procedures reliably achieve acceptance criteria under normal operating conditions [46].

The validation protocol should specify sampling locations with scientific rationale, acceptance criteria based on health-based limits, and documentation requirements [47]. Equipment grouping and product grouping strategies can reduce the validation burden when scientifically justified, using worst-case approaches for both soil difficulty and product toxicity [48].

6.3. Stage 3: Continued Process Verification

Continued process verification provides ongoing assurance that cleaning validation remains in a state of control throughout the product lifecycle [49]. Implementation of process controls including change control, preventive maintenance, and corrective and preventive action systems maintains the validated state [42]. Critical cleaning parameters—such as cleaning agent concentration, contact time, temperature, and rinse water conductivity—should be trended to detect process drift before it results in failures [50].

Ongoing Process Verification represents a data-driven approach that leverages Process Analytical Technologies for real-time monitoring of critical process parameters [51]. This continuous monitoring approach enables early detection of potential issues and supports predictive quality management [52].

7. Cross-Contamination Control in Multi-Product Facilities

7.1. Sources and Prevention of Cross-Contamination

Cross-contamination in pharmaceutical manufacturing can occur through multiple pathways: airborne transfer via inadequate HVAC controls, equipment surfaces with inadequate cleaning, personnel movement between production areas, and shared utilities [53]. Effective contamination control requires a comprehensive strategy addressing facility design, equipment dedication decisions, cleaning validation, and operational procedures [54].

 doi:10.20944/preprints202511.2242.v1

Product and material risk profiles must be understood, including assessment of safety and the potential impact of adverse effects resulting from cross-contamination [55]. High-risk product classes typically include antibiotics (particularly beta-lactams), microbial spore formers, immunological products, hormones, cytotoxics, and highly active products [55]. These may require dedicated equipment, special procedures, dedicated air handling, or dedicated facilities depending on the risk assessment outcome [56].

7.2. Equipment Train Concept

The equipment train concept addresses the cumulative effect of residues across the entire sequence of equipment used in product manufacture [57]. Acceptance criteria must be defined for the whole equipment train, not just individual pieces of equipment [57]. The Total Shared Surface area is used in MACO calculations to distribute the allowable carryover across all product-contact surfaces [14].

For processes with purification steps, such as biopharmaceutical manufacturing, the equipment train may be divided at the last purification step, with different cleaning strategies applied to upstream and downstream equipment [57]. This risk-based approach recognizes that purification steps provide inherent contamination control that can be factored into the overall cleaning strategy [58].

8. Discussion and Future Directions

The transition from compliance-based to risk-based cleaning validation represents a fundamental shift in how the pharmaceutical industry approaches contamination control. This evolution has been driven by regulatory expectations, scientific advances in toxicological risk assessment, and recognition that traditional arbitrary limits provided neither adequate protection nor efficient resource utilization [59].

Implementation challenges remain, particularly for organizations transitioning from legacy approaches. The requirement for toxicological expertise to derive health-based exposure limits, investment in analytical capabilities for lower-level detection, and cultural change toward continuous improvement rather than point-in-time validation all present barriers [60]. However, the benefits—including scientifically justified limits, more efficient resource allocation, and enhanced patient safety—justify the investment [61].

Emerging trends include increased use of digital technologies for data collection and trending, application of machine learning for predictive cleaning performance, and development of in-line monitoring technologies that could enable real-time release of cleaned equipment [62]. The integration of cleaning validation into broader contamination control strategies, as emphasized in EU GMP Annex 1, reflects recognition that cleaning is one element of a comprehensive approach to product quality assurance [63].

9. Conclusions

Risk-based cleaning validation represents the current standard for pharmaceutical manufacturing, supported by ICH Q9 quality risk management principles and health-based exposure limit methodologies. The approach requires scientific justification for acceptance criteria, systematic risk assessment of cleaning procedures, and ongoing verification of cleaning performance throughout the product lifecycle.

Key elements of effective risk-based cleaning validation include derivation of health-based exposure limits by qualified toxicologists, systematic risk assessment using tools such as FMEA, validated sampling and analytical methods with demonstrated recovery, worst-case product determination based on both cleanability and toxicity, and continued process verification with trending of critical parameters. By implementing these elements within a lifecycle approach,

 doi:10.20944/preprints202511.2242.v1

pharmaceutical manufacturers can ensure their cleaning validation programs effectively protect patient safety while optimizing operational efficiency.

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References

1. [1] Walsh, A. (2011). Cleaning validation for the 21st century: Acceptance limits for active pharmaceutical ingredients (APIs): Part I. *Pharmaceutical Engineering*, 31(4), 74-83. https://ispe.org/pharmaceutical-engineering/july-august-2011
2. [2] International Society for Pharmaceutical Engineering. (2010). *Baseline guide: Risk-based manufacture of pharmaceutical products (Risk-MaPP)*. ISPE. https://ispe.org/publications/guidance-documents/risk-mapp
3. [3] Walsh, A., Ovais, M., & Altmann, T. (2018). Introduction to science- and risk-based cleaning validation using ASTM E3106 & E3219. *Pharmaceutical Online*. https://www.pharmaceuticalonline.com/doc/introduction-to-science-and-risk-based-cleaning-validation-using-astm-e-e-0001
4. [4] International Council for Harmonisation. (2005). *ICH Q9: Quality risk management*. ICH. https://database.ich.org/sites/default/files/Q9_Guideline.pdf
5. [5] Sharnez, R., Lathia, J., Engstrom, R., & Gaughan, E. (2016). The regulatory framework for preventing cross-contamination of pharmaceutical products: History and considerations for the future. *Regulatory Toxicology and Pharmacology*, 79, S1-S14. https://doi.org/10.1016/j.yrtph.2016.05.013
6. [6] European Commission. (2015). *EudraLex Volume 4, Annex 15: Qualification and validation*. European Commission. https://health.ec.europa.eu/system/files/2016-11/2015-10_annex15_0.pdf
7. [7] International Council for Harmonisation. (2022). *ICH Q9(R1): Quality risk management (revision 1)*. ICH. https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guideline_Step4_2022_1219.pdf
8. [8] Martin, K. C., & Perez, A. (2008). Risk-based cleaning validation. *Pharmaceutical Engineering*, 28(3), 1-12. https://ispe.org/sites/default/files/attachments/public/May-June-2008.pdf
9. [9] European Medicines Agency. (2014). Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities (EMA/CHMP/CVMP/SWP/169430/2012). EMA. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-setting-health-based-exposure-limits-use-risk-identification-manufacture-different-medicinal-products-shared-facilities_en.pdf
10. [10] World Health Organization. (2021). Points to consider when including health-based exposure limits setting in cleaning validation. *WHO Technical Report Series*, No. 1033, Annex 2. https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/inspections/trs1033-annex2-points-to-consider-when-incl-hbels-in-cleaning-validation.pdf
11. [11] Naumann, B. D., & Sargent, E. V. (2010). Setting occupational exposure limits for pharmaceuticals. *Occupational Medicine*, 60(7), 509-513. https://doi.org/10.1093/occmed/kqq110
12. [12] Dolan, D. G., Naumann, B. D., Sargent, E. V., Maier, A., & Dourson, M. (2005). Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. *Regulatory Toxicology and Pharmacology*, 43(1), 1-9. https://doi.org/10.1016/j.yrtph.2005.06.010
13. [13] ASTM International. (2018). ASTM E3106-18: Standard guide for science-based and risk-based cleaning process development and validation. ASTM. https://www.astm.org/e3106-18e01.html
14. [14] Active Pharmaceutical Ingredients Committee. (2021). *Guidance on aspects of cleaning validation in active pharmaceutical ingredient plants*. APIC/CEFIC. https://apic.cefic.org/wp-content/uploads/2021/09/APIC_Cleaning-validation-guide_2021.pdf
15. [15] Stamatis, D. H. (2003). *Failure mode and effect analysis: FMEA from theory to execution* (2nd ed.). ASQ Quality Press. ISBN: 0873895983
16. [16] American Society for Quality. (2023). *Failure mode and effects analysis (FMEA)*. ASQ. https://asq.org/quality-resources/fmea

 doi:10.20944/preprints202511.2242.v1

17. [17] Kmenta, S., & Ishii, K. (2004). Scenario-based failure modes and effects analysis using expected cost. *Journal of Mechanical Design*, 126(6), 1027-1035. https://doi.org/10.1115/1.1799614
18. [18] Sankar, N. R., & Prabhu, B. S. (2001). Modified approach for prioritization of failures in a system failure mode and effects analysis. *International Journal of Quality & Reliability Management*, 18(3), 324-336. https://doi.org/10.1108/02656710110383737
19. [19] The Pharma Vision. (2024). 6 steps of FMEA (Failure Mode Effects Analysis). *The Pharma Vision*. https://thepharmavision.com/6-steps-of-failure-mode-effects-analysis-fmea/
20. [20] Cagliano, A. C., Grimaldi, S., & Rafele, C. (2011). A systemic methodology for risk management in healthcare sector. *Safety Science*, 49(5), 695-708. https://doi.org/10.1016/j.ssci.2011.01.006
21. [21] Ecolab. (2023). Designing a risk-based cleaning validation process. *Ecolab Life Sciences*. https://en-uk.ecolab.com/articles/2023/10/designing-a-risk-based-cleaning-validation-process
22. [22] Pharmaceutical Inspection Co-operation Scheme. (2007). Recommendations on validation master plan, installation and operational qualification, non-sterile process validation, cleaning validation (PI 006-3). PIC/S. https://picscheme.org/docview/1947
23. [23] Food and Drug Administration. (2023). *Q9(R1) Quality risk management guidance for industry*. FDA. https://www.fda.gov/media/167721/download
24. [24] Leucine. (2025). MACO calculation in cleaning validation: A complete guide. *Leucine Cleaning Validation*. https://www.leucine.io/cleaning-validation-blogs/maco-calculation-in-cleaning-validation-a-complete-guide
25. [25] Sharma, P. (2021). Automating MACO calculations in cleaning validation. *Pharmaceutical Engineering*. https://ispe.org/pharmaceutical-engineering/march-april-2021/automating-maco-calculations-cleaning-validation
26. [26] Health Canada. (2021). *Cleaning validation guide* (GUI-0028). Health Canada. https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/validation/cleaning-validation-guidelines-guide-0028.html
27. [27] Walsh, A. (2016). Cleaning limits—Why the 10-ppm and 0.001-dose criteria should be abandoned. *Pharmaceutical Technology*, 40(8), 34-40. https://www.pharmtech.com/view/cleaning-limits-why-10-ppm-and-0001-dose-criteria-should-be-abandoned
28. [28] Patel, B., & Patel, J. (2025). Comparative assessment of Levodopa and Carbidopa cleanability from stainless steel surfaces: A risk-based approach for pharmaceutical cleaning validation. *World Journal of Advanced Research and Reviews*, 28(01), 1960-1966. https://doi.org/10.30574/wjarr.2025.28.1.3653
29. [29] Forsyth, R. J., & Van Nostrand, V. (2004). Visible residue limit for cleaning validation and its potential application in a pharmaceutical research facility. *Pharmaceutical Technology*, 28(10), 58-72. https://www.pharmtech.com/view/visible-residue-limit-cleaning-validation-and-its-potential-application-pharmaceutical-research-facility
30. [30] Forsyth, R. J., & Van Nostrand, V. (2005). Application of visible-residue limit for cleaning validation in a pharmaceutical manufacturing facility. *Pharmaceutical Technology*, 29(10), 152-161. https://www.pharmtech.com/view/application-visible-residue-limit-cleaning-validation
31. [31] Forsyth, R. J., Hartman, J., & Van Nostrand, V. (2007). Risk-management assessment of visible-residue limits in cleaning validation. *Pharmaceutical Technology*, 31(3), 134-146. https://www.pharmtech.com/view/risk-management-assessment-visible-residue-limits-cleaning-validation
32. [32] Forsyth, R. J. (2009). Do visible residue limits make the 10-ppm carryover limit obsolete? *Pharmaceutical Technology*, 33(5), 106-115. https://www.pharmtech.com/view/do-visible-residue-limits-make-10-ppm-carryover-limit-obsolete
33. [33] Ecolab. (2024). Establishing effective visual residue limits in cleaning validation. *Ecolab Life Sciences*. https://www.ecolab.com/articles/2024/06/establishing-effective-visual-residue-limits-in-cleaning-validation
34. [34] Food and Drug Administration. (1993). *Guide to inspection of validation of cleaning processes*. FDA. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/validation-cleaning-processes-793

 doi:10.20944/preprints202511.2242.v1

35. [35] Pharma Tutor. (2020). A review on swab sampling and rinse sampling procedure used in pharmaceutical industry. *Pharma Tutor*. https://www.pharmatutor.org/articles/a-review-on-swab-sampling-and-rinse-sampling-procedure-used-in-pharmaceutical-industry
36. [36] Adebayo, O. I., & Okonkwo, A. C. (2025). Cleaning validation in pharmaceutical quality control laboratories: A structured protocol for contamination risk mitigation. *Heliyon*, 11(1), e41234. https://pmc.ncbi.nlm.nih.gov/articles/PMC12229404/
37. [37] Lamei Ramandi, S., Souri, E., Moghimi, H. R., & Hajimahmoodi, M. (2020). Evaluation of swab and rinse sampling procedures and recovery rate determination in cleaning validation considering various surfaces, amount and nature of the residues and contaminants. *Iranian Journal of Pharmaceutical Research*, 19(3), 383-390. https://doi.org/10.22037/ijpr.2020.112347.13830
38. [38] LeBlanc, D. A. (2020). Dispelling cleaning validation myths: Part I. *Pharmaceutical Technology*, 44(1), 24-30. https://www.pharmtech.com/view/dispelling-cleaning-validation-myths-part-i
39. [39] Ovais, M., Walsh, A., & Altmann, T. (2020). Qualification of a swab sampling procedure for cleaning validation. *Pharmaceutical Technology*, 44(7), 38-45. https://www.pharmtech.com/view/qualification-swab-sampling-procedure-cleaning-validation-0
40. [40] European Pharmaceutical Review. (2018). Test method validation for cleaning validation samples. *European Pharmaceutical Review*. https://www.europeanpharmaceuticalreview.com/article/1112/test-method-validation-for-cleaning-validation-samples/
41. [41] Forsyth, R. J. (2021). Rethinking limits in cleaning validation. *Pharmaceutical Technology*, 45(11), 28-34. https://www.pharmtech.com/view/rethinking-limits-cleaning-validation
42. [42] Lopolito, P., & Rivera, E. (2016). Cleaning validation in continuous manufacturing. *Pharmaceutical Technology*, 40(11), 34-42. https://www.pharmtech.com/view/cleaning-validation-continuous-manufacturing
43. [43] International Society for Pharmaceutical Engineering. (2023). Life-cycle approach to cleaning topical drug products. *Pharmaceutical Engineering*. https://ispe.org/pharmaceutical-engineering/january-february-2023/life-cycle-approach-cleaning-topical-drug-products
44. [44] Walsh, A., & Crevoisier, M. (2022). Cleaning process development: Cleanability testing and "hardest-to-clean" pharmaceutical products. *Pharmaceutical Online*. https://www.pharmaceuticalonline.com/doc/cleaning-process-development-cleanability-testing-and-hardest-to-clean-pharmaceutical-products-0001
45. [45] Forsyth, R. J. (2023). Cleanability of pharmaceutical soils from different materials of construction. *Pharmaceutical Technology*, 47(3), 32-40. https://www.pharmtech.com/view/cleanability-pharmaceutical-soils-different-materials-construction
46. [46] Pharma Guideline. (2025). Sampling in cleaning validation in pharmaceutical industry. *Pharma Guideline*. https://www.pharmaguideline.com/2017/06/sampling-cleaning-validation.html
47. [47] GMP Compliance. (2019). Cleaning validation: What can a quality risk management approach look like? *ECA Academy*. https://www.gmp-compliance.org/gmp-news/cleaning-validation-what-can-a-quality-risk-management-approach-look-like
48. [48] International Society for Pharmaceutical Engineering. (2021). Cleaning validation program maintenance in a process life-cycle model. *Pharmaceutical Engineering*. https://ispe.org/pharmaceutical-engineering/january-february-2021/cleaning-validation-program-maintenance-process
49. [49] Forsyth, R. J., & Imamoglu, S. (2022). Continued process verification for cleaning validation—Challenges and pitfalls. *Pharmaceutical Technology*, 46(1), 34-37. https://www.pharmtech.com/view/continued-process-verification-for-cleaning-validation-challenges-and-pitfalls
50. [50] International Society for Pharmaceutical Engineering. (2025). *Guide: Cleaning validation lifecycle—Applications, methods, & controls*. ISPE. https://ispe.org/publications/guidance-documents/guide-cleaning-validation-lifecycle-applications-methods-controls
51. [51] Ecolab. (2024). Embracing ongoing process verification in cleaning validation. *Ecolab Life Sciences*. https://en-uk.ecolab.com/articles/2024/07/embracing-ongoing-process-verification-in-cleaning-validation

 doi:10.20944/preprints202511.2242.v1

52. [52] ValGenesis. (2025). Risk-based cleaning validation: A lifecycle approach. *ValGenesis Blog*. https://www.valgenesis.com/blog/risk-based-cleaning-validation-a-lifecycle-approach
53. [53] GMP Insiders. (2025). Contamination, cross-contamination, and mix-ups in GMP. *GMP Insiders*. https://gmpinsiders.com/contamination-cross-contamination-and-mix-ups-in-pharmaceutical-manufacturing/
54. [54] Bagade, S. (2021). White paper: Prevention of contamination and cross-contamination in shared pharmaceutical manufacturing facilities. *Academia*. https://www.academia.edu/51948035/White_paper_Prevention_of_Contamination_and_Cross_Contamination_in_shared_Pharmaceutical_Manufacturing_Facilities
55. [55] BioPharm International. (2023). New challenges to the cleanroom paradigm for multi-product facilities. *BioPharm International*. https://www.biopharminternational.com/view/new-challenges-cleanroom-paradigm-multi-product-facilities
56. [56] Pharmaceutical Technology. (2023). Preventing cross-contamination in multi-product facilities. *Pharmaceutical Technology*. https://www.pharmaceutical-technology.com/sponsored/preventing-cross-contamination-in-multi-product-facilities/
57. [57] Association pour le développement du management de la qualité dans les industries pharmaceutiques et cosmétiques. (2020). Health-based approach implementation for setting limits in cleaning validation for vaccines/biotech. *A3P*. https://www.a3p.org/en/health-based-approach-implementation-for-setting-limits-in-cleaning-validation-for-vaccinesbiotech-vague-54/
58. [58] Pharmaceutical Inspection Co-operation Scheme. (2022). *Cross-contamination in shared facilities*. PIC/S. https://picscheme.org/docview/2270
59. [59] Pharmaceutical Online. (2020). Replacing the MAC/MACO with the MSC: Rethinking how cleaning validation limits are calculated. *Pharmaceutical Online*. https://www.outsourcedpharma.com/doc/replacing-the-mac-maco-with-the-msc-rethinking-how-cleaning-validation-limits-are-calculated-0001
60. [60] Novatek International. (2021). Cleaning validation frequently asked questions. *Novatek International*. https://ntint.com/product/cleaning-validation-frequently-asked-questions/
61. [61] Pharma Digests. (2023). Cleaning validation acceptance criteria calculation. *Pharma Digests*. https://pharmadigests.com/cleaning-validation-acceptance-criteria-calculation/
62. [62] Pharmaceutical Online. (2024). Ongoing process verification: A data-driven approach to cleaning validation. *Pharmaceutical Online*. https://www.pharmaceuticalonline.com/doc/ongoing-process-verification-a-data-driven-approach-to-cleaning-validation-0001
63. [63] European Commission. (2022). *EudraLex Volume 4, Annex 1: Manufacture of sterile medicinal products*. European Commission. https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en