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The paradigm shifts in cleaning validation: From arbitrary limits to science-based patient safety

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Abstract

Cleaning validation has undergone a significant paradigm shift over the past three decades, evolving from prescriptive, arbitrary acceptance criteria to sophisticated risk-based methodologies grounded in toxicological science. This comprehensive review traces the evolution of cleaning validation practices from their inception in the late 1980s through the current era of health-based exposure limits. The transformation has been driven by regulatory advancements, including the United States Food and Drug Administration's (FDA) early guidance documents, the International Council for Harmonisation (ICH) quality guidelines (Q9, Q10, Q12), and the European Medicines Agency's (EMA) landmark 2014 guideline on setting health-based exposure limits. This review examines the transition from traditional acceptance criteria based on fractions of therapeutic doses and analytical detection limits to scientifically justified limits derived from Acceptable Daily Exposure (ADE) and Permitted Daily Exposure (PDE) values. Risk assessment methodologies including Failure Mode and Effects Analysis (FMEA), Hazard Analysis and Critical Control Points (HACCP), and risk ranking tools are critically evaluated for their application in cleaning validation programs. The mathematical frameworks for calculating Maximum Allowable Carryover (MACO) using both traditional and health-based approaches are presented and compared. Analytical method considerations, including Total Organic Carbon (TOC) analysis, High-Performance Liquid Chromatography (HPLC), and swab recovery validation, are discussed within the context of risk-based strategies. Implementation challenges, including equipment grouping, worst-case selection, and lifecycle management, are addressed. The review concludes with an examination of emerging trends, including the integration of Quality Risk Management (QRM) principles, continuous process verification, and the application of data integrity requirements to cleaning validation documentation. This evolution represents a maturation of pharmaceutical quality systems toward science-based and patient-focused manufacturing practices.

Keywords: Cleaning validation; Risk-based approach; Health-based exposure limits; Permitted Daily Exposure; Acceptable Daily Exposure; Quality Risk Management; Pharmaceutical manufacturing; Cross-contamination

1. Introduction

Cleaning validation represents a critical element of Good Manufacturing Practice (GMP) in pharmaceutical, biotechnology, and medical device manufacturing, serving as a fundamental control measure to prevent cross-contamination between products manufactured using shared equipment [1]. The principle underlying cleaning validation is straightforward: manufacturers must demonstrate through documented evidence that cleaning procedures consistently remove residues of active pharmaceutical ingredients (APIs), excipients, cleaning agents, and

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microbial contamination to predetermined acceptable levels [2]. However, the methodologies for establishing these acceptable levels and the scientific rigor applied to validation studies have undergone profound transformation since the concept's formal introduction in regulatory frameworks.

The genesis of cleaning validation as a regulatory expectation can be traced to contamination incidents in the pharmaceutical industry during the 1980s, most notably cross-contamination events that resulted in patient harm and product recalls. These incidents highlighted the inadequacy of visual inspection alone as a means of verifying equipment cleanliness and prompted regulatory authorities to demand more rigorous, documented approaches to cleaning verification. The response from industry and regulators alike was the development of cleaning validation programs, initially characterized by conservative, often arbitrary acceptance criteria designed to provide substantial safety margins.

The traditional approach to cleaning validation, which dominated pharmaceutical manufacturing from the early 1990s through the mid-2010s, relied primarily on three types of acceptance criteria: fractions of therapeutic doses (typically 1/1000th of the minimum daily dose), analytical detection limits (frequently 10 parts per million), and visual cleanliness standards [3]. While these criteria provided practical benchmarks for validation studies, they lacked a consistent scientific foundation and often resulted in either unnecessarily stringent limits for low-toxicity compounds or potentially inadequate limits for highly potent substances [4].

The paradigm shift toward risk-based cleaning validation emerged from the convergence of several developments: the maturation of Quality Risk Management (QRM) principles codified in ICH Q9 [5], advancements in toxicological science enabling the determination of health-based exposure limits [6], and regulatory recognition that one-size-fits-all approaches failed to adequately protect patients from highly hazardous compounds while simultaneously imposing disproportionate burdens for benign substances [7]. This evolution reflects a broader trend in pharmaceutical regulation toward science-based, risk-proportionate quality systems.

The objective of this comprehensive review is to trace the evolution of cleaning validation from its inception to the current state of practice, with particular emphasis on the transition to risk-based methodologies. This review examines the historical development of cleaning validation concepts, the evolution of regulatory frameworks across major jurisdictions, the scientific basis for health-based exposure limits, risk assessment tools and their application, mathematical frameworks for limit calculations, analytical method considerations, and implementation challenges. By synthesizing the extensive literature and regulatory guidance on this topic, this review aims to provide practitioners with a consolidated resource for understanding and implementing contemporary risk-based cleaning validation programs.

2. Historical Development of Cleaning Validation

2.1. Origins and Early Concepts (Pre-1990)

Prior to the formal establishment of cleaning validation requirements, pharmaceutical manufacturers relied primarily on visual inspection and general cleanliness standards derived from food industry practices [8]. Equipment cleaning was considered a routine operational activity rather than a validated process requiring documented evidence of effectiveness. The assumption prevailed that if equipment appeared clean and products met their specifications, the cleaning process was adequate.

The limitations of this approach became apparent through several contamination incidents that occurred during the 1980s. While specific incident details remain partially confidential due to litigation considerations, regulatory inspection findings from this era documented instances of cross-contamination resulting from inadequate cleaning between product changeovers [9]. These incidents demonstrated that visually clean equipment could harbor significant residues of active substances, particularly in hard-to-clean areas such as gaskets, valves, and dead legs in piping systems.

2.2. Emergence of Formal Requirements (1990-2000)

The United States Food and Drug Administration published its seminal "Guide to Inspections of Validation of Cleaning Processes" in 1993, marking the first comprehensive regulatory guidance specifically addressing cleaning validation [9]. This document established fundamental principles that would influence cleaning validation practices for the subsequent two decades. The FDA guide introduced the concept of establishing acceptance limits based on scientific rationale and documented the expectation that cleaning procedures be validated rather than merely verified.

The 1993 FDA guide proposed three approaches for establishing acceptance limits that became industry standards: (a) the dose criterion, limiting carryover to no more than 0.1% (1/1000th) of the minimum therapeutic dose of any product appearing in the maximum daily dose of the subsequent product; (b) the analytical criterion, typically set at 10 ppm of any product appearing in another product; and (c) the visual criterion, requiring no visible residue after cleaning [9]. Manufacturers were expected to apply the most stringent of these criteria.

Concurrently with FDA guidance development, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and its predecessor organizations began addressing cleaning validation in European regulatory frameworks. The PIC/S document PI 006, first issued in 2004 but reflecting practices developed during the 1990s, provided recommendations for cleaning validation that largely aligned with FDA expectations while incorporating European perspectives on documentation and lifecycle management [10].

2.3. Maturation of Traditional Approaches (2000-2010)

The decade following the initial regulatory guidance saw widespread implementation of cleaning validation programs across the pharmaceutical industry. Industry organizations, including the International Society for Pharmaceutical Engineering (ISPE) and the Parenteral Drug Association (PDA), published technical guides and best practice documents that helped standardize approaches [11, 12]. The ISPE Baseline Guide on Cleaning and Cleaning Validation, published in various editions during this period, provided practical implementation guidance that complemented regulatory requirements.

During this era, the traditional acceptance criteria became deeply embedded in industry practice. The 1/1000th dose criterion and the 10 ppm limit were applied almost universally, regardless of the toxicological properties of the substances involved. This approach, while providing regulatory compliance and practical simplicity, began to show limitations as the industry's product portfolio evolved to include an increasing proportion of highly potent active pharmaceutical ingredients (HPAPIs).

Research conducted during this period began to challenge the adequacy of traditional limits for potent compounds. Fourman and Mullen's influential work on cleaning validation, while supporting the general framework, acknowledged that modifications might be necessary for compounds with unusual potency or toxicity [3]. Studies evaluating actual cleaning performance demonstrated that while traditional limits were readily achievable for most conventional small molecule APIs, they might be inadequate for compounds with therapeutic doses in the microgram range.

2.4. Recognition of Limitations

By the late 2000s, the pharmaceutical industry and regulatory authorities increasingly recognized that traditional cleaning validation approaches suffered from significant scientific limitations. The 1/1000th dose criterion assumed that exposure to this fraction of a therapeutic dose would be safe, but this assumption lacked toxicological foundation for compounds with dose-response relationships differing from their intended therapeutic effects. For example, a compound might be therapeutically effective at a certain dose while exhibiting carcinogenic, teratogenic, or sensitizing effects at much lower doses.

The 10 ppm criterion represented an arbitrary analytical convenience rather than a health-based standard. For a highly potent compound with a therapeutic dose of 10 micrograms and the subsequent product having a daily dose of 1 gram, the 10 ppm limit would allow 10 micrograms of contamination—equivalent to a full therapeutic dose [6]. Conversely, for a relatively benign excipient, the 10 ppm limit might impose unnecessary analytical burden without corresponding safety benefit.

These limitations became increasingly problematic as biologics, highly potent oncology compounds, and other specialized therapies became more prevalent in pharmaceutical manufacturing. The stage was set for a fundamental reconsideration of the scientific basis for cleaning validation acceptance limits.

3. Evolution of Regulatory Framework

3.1. ICH Quality Guidelines: Foundation for Risk-Based Approaches

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published a series of quality guidelines during the 2000s that, while not specifically addressing cleaning validation, established the conceptual framework for risk-based approaches that would later transform the field.

ICH Q9, "Quality Risk Management," published in 2005 and subsequently revised, provided a systematic framework for the assessment, control, communication, and review of risks to quality throughout the pharmaceutical product lifecycle [5]. The guideline introduced formal risk assessment tools including Failure Mode and Effects Analysis (FMEA), Fault Tree Analysis (FTA), and Hazard Analysis and Critical Control Points (HACCP) to pharmaceutical quality systems. Although cleaning validation was not specifically addressed, Q9 established the principle that quality-related activities should be proportionate to the risks involved—a concept directly applicable to cleaning validation program design.

ICH Q10, "Pharmaceutical Quality System," published in 2008, complemented Q9 by describing a comprehensive quality management system model that emphasized lifecycle management and continual improvement [13]. The guideline's emphasis on process performance monitoring and knowledge management provided a framework for treating cleaning validation not as a one-time compliance exercise but as an ongoing commitment requiring periodic reassessment as new information became available.

ICH Q12, "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management," published in 2019, further reinforced lifecycle concepts and introduced mechanisms for managing post-approval changes, including those affecting cleaning procedures [14]. The guideline's provisions for established conditions and post-approval change management protocols have implications for maintaining cleaning validation in a state of compliance throughout a product's commercial life.

3.2. EMA Guideline on Health-Based Exposure Limits (2014)

The European Medicines Agency's publication of the "Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities" in November 2014 represented a watershed moment in cleaning validation evolution [7]. Effective March 2015, this guideline fundamentally changed the regulatory expectation for establishing cleaning validation acceptance limits in European Union member states and, through regulatory convergence, influenced global practices.

The EMA guideline mandated that cleaning limits be established based on health-based exposure limits, specifically the Permitted Daily Exposure (PDE), derived through formal toxicological assessment. The PDE represents the maximum acceptable daily intake of a residual substance that is unlikely to cause adverse health effects in the exposed population, including sensitive subpopulations. This approach replaced the arbitrary 1/1000th dose criterion with a scientifically justified limit based on the actual hazard profile of the substance.

The guideline specified that PDEs should be established considering: (a) pharmacological effects and dose-response relationships; (b) toxicological data including acute, repeat-dose, reproductive, developmental, and genetic toxicity; (c) carcinogenic potential; (d) sensitization potential; and (e) any other relevant toxicological endpoints [7]. For established drugs with extensive clinical data, the PDE might be derived from the No Observed Adverse Effect Level (NOAEL) in clinical studies; for compounds with limited clinical data, derivation from preclinical toxicology studies was required.

3.3. FDA Perspectives and Guidance

The United States Food and Drug Administration, while not issuing guidance as prescriptive as the EMA's regarding health-based limits, progressively incorporated risk-based concepts into its inspection and enforcement approaches. FDA investigators began asking more probing questions about the scientific justification for cleaning limits during facility inspections, particularly for facilities manufacturing highly potent compounds [15].

The FDA's 2011 Process Validation guidance, while focused on process validation generally, reinforced the importance of risk-based approaches and lifecycle management that could be extrapolated to cleaning validation [16]. The guidance emphasized that validation should be "based on sound science" and that manufacturers should have a "thorough understanding of the product and process."

FDA's increased scrutiny of cleaning validation for dedicated versus multi-product facilities intensified following several high-profile cross-contamination incidents involving hormonal and cytotoxic products. Warning letters and Form 483 observations from this period documented expectations for risk assessments, scientifically justified limits, and ongoing monitoring that aligned with emerging risk-based approaches.

3.4. WHO and Global Regulatory Perspectives

The World Health Organization published its Technical Report Series 937, Annex 4, addressing cleaning validation in 2006, with subsequent updates reflecting evolving expectations [2]. While initially aligned with traditional approaches,

WHO guidance has progressively incorporated references to risk-based methodologies and health-based limits, acknowledging the EMA guideline as a reference for establishing acceptable limits.

Health Canada, the Therapeutic Goods Administration (TGA) of Australia, and other regulatory authorities have similarly evolved their expectations, generally moving toward acceptance of or requirements for health-based exposure limits. The International Pharmaceutical Regulators Forum and bilateral mutual recognition agreements have facilitated regulatory convergence on these concepts [17].

3.5. Industry Standards and Guidance Documents

Industry organizations have published numerous guidance documents supporting implementation of risk-based cleaning validation approaches. The ISPE Risk-MaPP (Risk-Based Manufacture of Pharmaceutical Products) Guide, published in 2010, provided comprehensive guidance on applying risk management principles to cross-contamination control, including cleaning validation [11]. This guide introduced the concept of the Acceptable Daily Exposure (ADE), synonymous with PDE, and provided frameworks for integrating exposure limits into facility and cleaning program design.

ASTM International published E3106, "Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation," in 2018 [18]. This standard provided detailed guidance on implementing health-based exposure limits and risk assessment methodologies in cleaning validation programs. ASTM E3106 represented a significant milestone as the first consensus standard specifically addressing risk-based cleaning validation.

The Parenteral Drug Association published Technical Report No. 29, "Points to Consider for Cleaning Validation," in revised editions that progressively incorporated risk-based concepts [12]. PDA Technical Report No. 49, addressing biologics manufacturing, similarly addressed cleaning validation with consideration for the unique risks posed by biological products [19].

4. Risk Assessment Methodologies in Cleaning Validation

4.1. Quality Risk Management Principles

The application of Quality Risk Management (QRM) to cleaning validation requires a structured approach to identifying, analyzing, evaluating, and controlling risks associated with residual contamination. ICH Q9 provides the foundational framework, emphasizing that QRM processes should be commensurate with the risks and based on scientific knowledge and ultimately linked to patient protection [5].

In the cleaning validation context, QRM principles guide several critical decisions: determining which products and equipment require validation, establishing the scope and rigor of validation studies, setting acceptance limits, determining sampling strategies, and establishing ongoing monitoring programs. The risk assessment should consider both the probability of cleaning failure and the severity of consequences should contamination occur [20].

Risk factors in cleaning validation include product-related factors (potency, toxicity, solubility, cleanability), process-related factors (cleaning procedure design, equipment complexity, manual versus automated cleaning), and facility-related factors (equipment dedication, campaign length, production sequence). A comprehensive risk assessment evaluates all these factors to develop a cleaning validation strategy proportionate to actual risks.

4.2. Failure Mode and Effects Analysis (FMEA)

Failure Mode and Effects Analysis (FMEA) represents one of the most widely applied risk assessment tools in cleaning validation programs. FMEA systematically evaluates potential failure modes of a cleaning process, their effects, and their causes to prioritize risk mitigation actions [21].

In cleaning validation FMEA, typical failure modes include: incomplete removal of product residues, incomplete removal of cleaning agent residues, inadequate drying allowing microbial growth, damage to equipment surfaces creating harborage sites, and documentation errors. For each failure mode, the FMEA evaluates severity (impact on patient safety and product quality), occurrence (probability of the failure mode), and detection (probability of detecting the failure before patient exposure) [22].

The Risk Priority Number (RPN), calculated as the product of severity, occurrence, and detection scores (Equation 1), provides a basis for prioritizing risk control measures:

Equation 1: *RPN = Severity × Occurrence × Detection*

Studies have demonstrated the utility of FMEA in optimizing cleaning validation programs. Research applying FMEA to cleaning validation for multi-product pharmaceutical manufacturing facilities demonstrated that the approach enabled more efficient resource allocation while maintaining patient safety. FMEA-guided prioritization has been shown to reduce validation effort significantly compared to traditional approaches while identifying previously unrecognized high-risk scenarios [4].

However, FMEA has limitations in the cleaning validation context. The subjective nature of scoring can lead to inconsistent results across assessors, and the multiplicative RPN calculation can obscure important risk factors. Some practitioners recommend using severity as the primary ranking criterion, with occurrence and detection serving as secondary factors.

4.3. Hazard Analysis and Critical Control Points (HACCP)

The Hazard Analysis and Critical Control Points (HACCP) methodology, originally developed for food safety, offers an alternative risk assessment framework for cleaning validation. HACCP focuses on identifying critical control points in a process where monitoring and control are essential to prevent, eliminate, or reduce hazards to acceptable levels [23].

Applied to cleaning validation, HACCP principles guide identification of critical cleaning parameters (time, temperature, chemical concentration, mechanical action), establishment of critical limits for these parameters, monitoring procedures to verify that critical limits are maintained, corrective actions when monitoring indicates deviation from critical limits, and verification activities to confirm the system is working as intended.

The HACCP approach is particularly valuable for designing cleaning processes and establishing in-process controls, as it encourages process understanding and proactive control rather than reliance on end-product testing alone.

4.4. Risk Ranking and Filtering

Risk ranking and filtering methodologies provide simplified approaches to risk assessment suitable for preliminary screening or situations where detailed FMEA is impractical. These methods typically involve categorizing products and equipment according to risk factors and applying predefined validation requirements to each category [18].

Product risk factors commonly used in ranking include: therapeutic category (oncology, hormonal, immunomodulatory products receiving higher risk classifications), potency (based on ADE/PDE values), clinical status (investigational products potentially receiving higher scrutiny due to incomplete safety data), and cleanability (based on physicochemical properties affecting removal). Equipment risk factors include complexity, cleanability, automation level, and shared versus dedicated status.

ASTM E3106 describes a risk ranking approach that categorizes products into hazard bands based on occupational exposure limits or PDEs [18]. Products are assigned to bands ranging from Band 1 (low hazard) to Band 5 (high hazard), with progressively more stringent cleaning validation requirements for higher bands. This approach provides a practical framework for large organizations managing diverse product portfolios.

4.5. Integration of Risk Assessment with Lifecycle Management

Contemporary risk-based cleaning validation integrates risk assessment with lifecycle management principles, recognizing that risks may change over time as new information becomes available or manufacturing conditions evolve [24]. This integration requires:

- **Periodic risk review:** Established risk assessments should be reviewed at defined intervals and whenever significant changes occur, including new toxicological data, changes to manufacturing processes, or observed cleaning failures.
- **Change control integration:** Changes to products, cleaning procedures, or equipment should trigger risk assessment review to evaluate whether existing cleaning validation remains adequate.
- **Trend monitoring:** Ongoing monitoring data should be analyzed for trends that might indicate changing risk profiles, even when individual results remain within specifications.

- **Knowledge management:** Risk assessments should be informed by accumulated process knowledge and updated as understanding of cleaning process capability improves.

5. Health-Based Exposure Limits

5.1. Concepts and Terminology

Health-based exposure limits represent the cornerstone of risk-based cleaning validation, replacing arbitrary fractions of therapeutic doses with limits derived from toxicological assessment. Two terms predominate in the literature: Acceptable Daily Exposure (ADE), used primarily in ISPE guidance, and Permitted Daily Exposure (PDE), used in EMA guidance [6, 7]. While nuanced differences exist in their derivation, the terms are often used interchangeably and represent the same fundamental concept: the maximum daily intake of a residual substance unlikely to cause adverse effects.

The ADE/PDE is calculated by identifying the critical effect (the adverse effect occurring at the lowest dose), determining the Point of Departure (PoD) for that effect (typically the No Observed Adverse Effect Level or NOAEL), and applying adjustment factors to account for uncertainties in extrapolating from study conditions to human exposure scenarios (Equation 2):

Equation 2: $ADE\ (or\ PDE) = NOAEL / (F1 \times F2 \times F3 \times F4 \times F5)$

Where the adjustment factors are:

- F1: Interspecies extrapolation (accounts for differences between study species and humans)
- F2: Intraspecies variability (accounts for variation within the human population)
- F3: Short-term to long-term exposure extrapolation
- F4: Severity factor (applied for severe toxicological endpoints)
- F5: Additional modifying factor (applied based on data quality or other considerations)

5.2. Toxicological Assessment and Data Sources

Establishing ADE/PDE values requires comprehensive toxicological assessment by qualified experts. The assessment draws from multiple data sources, prioritized by relevance to the human exposure scenario:

- Clinical data: For marketed pharmaceuticals, clinical safety data from controlled studies and post-marketing surveillance provide the most relevant information for human risk assessment. The NOAEL from clinical studies, when available, provides the most direct basis for ADE/PDE derivation.
- Preclinical toxicology: Regulatory toxicology studies conducted for drug approval (acute, repeat-dose, reproductive, developmental, genetic toxicity, and carcinogenicity studies) provide systematic evaluation of adverse effects across multiple endpoints and species.
- Published literature: Peer-reviewed toxicological literature supplements regulatory submissions and may provide additional mechanistic understanding.
- Structural analysis: For new compounds or those with limited data, structure-activity relationships and read-across from analogous compounds may inform preliminary assessments.

Research evaluating ADE values established for pharmaceutical compounds found that clinical data supported the derived values in the majority of cases, with remaining cases requiring adjustment based on preclinical findings not observed in clinical settings [25].

5.3. Adjustment Factors and Their Application

The adjustment factors (also termed uncertainty factors or safety factors) applied in ADE/PDE derivation account for uncertainties in the risk assessment and provide protective margins for sensitive populations. Standard default values exist for each factor, with modification permitted based on compound-specific data.

- **F1 (Interspecies):** Default values range from 1 (human data) to 12 (dog data) to 10 (rodent data), with pharmacokinetic data potentially supporting modified values.

- **F2 (Intraspecies):** A default value of 10 accounts for variation within the human population, including children, elderly, and individuals with genetic polymorphisms. For compounds with well-characterized pharmacokinetics and pharmacogenomics, this factor may be modified.
- **F3 (Duration):** Applied when the available study duration is shorter than the expected human exposure duration. Factors range from 1 to 10 depending on the specific circumstances.
- **F4 (Severity):** Applied for severe toxicological endpoints such as irreversible effects, teratogenicity, or non-genotoxic carcinogenicity. Factors up to 10 may be applied.
- **F5 (Additional):** A modifying factor applied when data quality is limited, mechanistic understanding is incomplete, or other concerns exist. This factor is applied conservatively and with scientific justification.

Analysis of the distribution of composite adjustment factors applied in establishing PDEs for EMA-reviewed products found that factors ranged from 100 to 100,000, with a geometric mean of approximately 5,000 [26]. This analysis highlighted the substantial protective margins incorporated in health-based limits.

5.4. Special Considerations for Hazardous Categories

Certain categories of compounds require special consideration in ADE/PDE derivation due to their unique toxicological profiles:

- **Genotoxic compounds:** Compounds with genotoxic potential are assumed to have no threshold for carcinogenic effects, requiring calculation of Threshold of Toxicological Concern (TTC) values or compound-specific risk assessment based on carcinogenic potency [27]. ICH M7 provides guidance on genotoxic impurities applicable to cleaning residue assessment.
- **Sensitizers:** Compounds causing immune-mediated sensitization may not follow traditional dose-response relationships, and establishing safe thresholds is challenging. Conservative limits and stringent process controls are typically required [28].
- **Biologics:** Biological products present unique challenges due to their size, complexity, and potential for immunogenicity. Traditional toxicological approaches may be insufficient, requiring consideration of biological activity, aggregation propensity, and immunogenic potential [19].
- **Reproductive toxicants:** Compounds affecting reproduction or development require particular attention to F4 severity factors and may necessitate lower limits than those based on other endpoints [29].

6. Implementation of Risk-Based Cleaning Validation

6.1. Calculating Maximum Allowable Carryover (MACO)

The Maximum Allowable Carryover (MACO) represents the maximum quantity of residue from a previous product that may be present on equipment surfaces after cleaning without posing unacceptable risk to patients receiving the subsequent product. MACO calculation translates the ADE/PDE into a practical limit applicable to specific manufacturing scenarios.

Traditional MACO Calculation:

The traditional MACO formula (Equation 3), still applicable in some jurisdictions and for non-potent compounds, is:

Equation 3: $MACO = (TD \times MBS \times SF) / LDD$

Where:

- TD = Minimum therapeutic dose of the previous product
- MBS = Minimum batch size of the next product
- SF = Safety factor (typically 0.001, representing 1/1000th)
- LDD = Largest daily dose of the next product

Health-Based MACO Calculation:

The health-based MACO formula (Equation 4) incorporates the ADE/PDE:

Equation 4: *MACO = (ADE × MBS) / LDD*

Where:

- ADE = Acceptable Daily Exposure (mg/day)
- MBS = Minimum batch size of the next product (kg)
- LDD = Largest daily dose of the next product (kg/day)

This calculation yields the total mass of residue permissible in the batch. Converting to surface concentration limits requires division by the total shared surface area (Equation 5):

Equation 5: *Surface Limit = MACO / SSA*

Where:

- SSA = Shared surface area of equipment train (cm^2)

6.2. Equipment Grouping and Worst-Case Selection

Risk-based cleaning validation employs equipment grouping and worst-case selection strategies to optimize validation efficiency while maintaining scientific rigor. These strategies are particularly important for multi-product facilities with extensive equipment inventories and product portfolios [30].

Equipment grouping involves categorizing equipment by cleaning characteristics, considering factors such as: materials of construction, geometry and cleanability, cleaning procedure applied, and product contact characteristics. Equipment within a group is expected to have equivalent cleaning performance, permitting validation of representative units rather than every individual piece.

Worst-case selection identifies the most challenging cleaning scenario within each group for validation, with the assumption that successful validation under worst-case conditions provides assurance for all other scenarios. Worst-case factors include:

- Product with poorest cleanability (lowest solubility, highest surface adhesion)
- Product with lowest ADE/PDE (most stringent limit)
- Equipment with most challenging geometry
- Maximum soil load
- Maximum hold time before cleaning

Validation studies conducted under these conditions provide the most conservative demonstration of cleaning effectiveness. Research has demonstrated that worst-case selection based on formalized risk assessment criteria can significantly reduce validation studies compared to validating all product/equipment combinations while maintaining equivalent patient safety margins.

6.3. Cleaning Process Design and Validation

Risk-based cleaning validation begins with science-based cleaning process design. Understanding the physicochemical properties of residues, their interactions with equipment surfaces, and the mechanisms of cleaning agent action enables development of effective, efficient cleaning procedures [31].

Critical cleaning parameters typically include:

- Time: Duration of cleaning agent contact and rinse cycles
- Action: Mechanical energy applied (agitation, spray pressure, scrubbing)
- Chemistry: Cleaning agent type, concentration, and activity
- Temperature: Impact on solubility and reaction kinetics

These parameters, often referred to as the "TACT" factors, should be optimized during development studies and controlled within validated ranges during routine operation.

Validation study design should reflect risk assessment findings. For high-risk products (low ADE, poor cleanability), more extensive validation may be appropriate, including:

- Increased number of validation runs (beyond the traditional three)
- Additional sampling locations
- Multiple analytical methods
- Challenge conditions beyond routine worst-case

For lower-risk products, reduced validation scope may be justified, potentially including bracketing approaches or reliance on ongoing monitoring data.

6.4. Sampling Strategies and Locations

Sampling strategy is a critical element of cleaning validation, as it determines the ability to detect residues and verify cleaning effectiveness. Two primary sampling methods are employed: swab (direct surface) sampling and rinse sampling, with visual inspection serving as a complementary technique [32].

Swab sampling provides direct measurement of residues on equipment surfaces and is generally preferred for accessible areas. Critical considerations include:

- Swab material and solvent selection for adequate recovery
- Sampling area definition (typically 25 cm^2 to 100 cm^2)
- Sampling technique standardization and training
- Recovery study validation (demonstrating acceptable recovery from representative surfaces)

Rinse sampling collects residues in the final rinse solution and is valuable for areas inaccessible to swabbing. Rinse sampling may underestimate surface residues and should be correlated with swab sampling where possible.

Risk-based sampling location selection prioritizes areas most likely to harbor residues or most critical for product quality:

- Hard-to-clean areas (valves, dead legs, seams)
- Areas with longest product contact
- Areas with most challenging geometry
- Locations with previous cleaning failures

Research has developed risk-based approaches to sampling location selection using criticality scoring that can reduce sampling locations while improving detection of problematic areas [33].

7. Analytical Considerations in Risk-Based Cleaning Validation

7.1. Analytical Method Selection

Selection of appropriate analytical methods is fundamental to cleaning validation success. The method must be capable of detecting residues at concentrations below acceptance limits with adequate precision, accuracy, and specificity [34]. Risk-based approaches influence method selection by enabling method complexity to be proportionate to the risks involved.

Common analytical methods for cleaning validation include:

- **Total Organic Carbon (TOC):** A non-specific method that measures all carbon-containing compounds, TOC is widely used for cleaning validation due to its speed, sensitivity, and applicability to diverse residues. TOC is particularly valuable for worst-case approaches, as it will detect any organic residue regardless of source. Limitations include inability to distinguish between product residues, cleaning agent residues, and other organic contamination [35].
- **High-Performance Liquid Chromatography (HPLC):** Specific methods provide unequivocal identification and quantification of target compounds. HPLC is preferred when specificity is required, particularly for potent

compounds where distinguishing the API from other residues is important. Method development and validation requirements make HPLC more resource-intensive than TOC [36].

- **UV-Visible Spectrophotometry:** Offers intermediate specificity between TOC and HPLC and may be suitable for compounds with distinctive chromophores.
- **Ion Chromatography:** Used for detection of cleaning agent residues, particularly for ionic surfactants and caustic/acidic residues.

7.2. Method Validation for Cleaning Applications

Analytical methods used in cleaning validation must be validated for their intended purpose, with validation parameters appropriate to cleaning sample matrices. Key validation parameters include [34]:

- **Specificity/Selectivity:** Demonstrated ability to detect the target analyte in the presence of potential interferences from cleaning agents, equipment materials, and other products.
- **Linearity and Range:** Established across a range encompassing the acceptance limit, typically from the limit of quantitation to at least 120% of the acceptance limit.
- **Accuracy:** Demonstrated through recovery studies from representative surfaces, with acceptable recovery typically ranging from 70% to 120% (swab methods) or higher for rinse methods.
- **Precision:** Repeatability and intermediate precision appropriate to the method's intended use.
- **Limit of Detection (LOD) and Limit of Quantitation (LOQ):** Sufficiently low to detect residues at concentrations well below acceptance limits, typically LOQ ≤ 50% of the acceptance limit.
- **Robustness:** Method performance stability across minor variations in method parameters.

Recovery studies deserve particular attention in cleaning method validation. Swab recovery from actual equipment surfaces, or representative coupons, must be established and used to correct analytical results. Research has demonstrated that recovery varies significantly with surface material, residue type, and drying time, emphasizing the need for realistic recovery study designs [37].

7.3. Analytical Method Considerations for Health-Based Limits

The transition to health-based limits presents analytical challenges, particularly for highly potent compounds with very low ADEs. When the calculated acceptance limit is below practical analytical detection capabilities, several approaches may be considered [38]:

- **Process-based controls:** Where analytical verification is impractical, reliance on validated cleaning processes with appropriate process controls may be justified through risk assessment.
- **Surrogate methods:** TOC or other non-specific methods may serve as surrogates when specific methods cannot achieve required sensitivity, provided the surrogate method can demonstrate adequate cleaning.
- **Enhanced analytical techniques:** LC-MS/MS and other highly sensitive techniques may achieve detection limits adequate for potent compound residues.
- **Surface limit adjustments:** Sampling larger areas or combining samples may effectively lower detection requirements while maintaining sample representativeness.

The risk assessment should document the rationale for the selected analytical approach and any limitations in the validation data that result from analytical constraints.

8. Challenges and Future Directions

8.1. Implementation Challenges

Despite the scientific advantages of risk-based cleaning validation, implementation presents significant challenges for many organizations [39]:

- **Toxicological expertise:** Establishing ADEs/PDEs requires specialized toxicological expertise that may not be available in-house. Organizations must either develop internal capabilities or engage external consultants, with associated costs and potential delays.
- **Legacy product assessment:** Retrospective establishment of ADEs for existing product portfolios requires substantial effort, particularly for older products with limited toxicological packages.
- **Regulatory harmonization:** Despite progress toward convergence, regulatory expectations vary across jurisdictions, creating complexity for global manufacturers.
- **Analytical capability:** Very low ADEs for potent compounds may challenge analytical detection capabilities, requiring investment in advanced instrumentation or alternative strategies.
- **Change management:** Transitioning from traditional to risk-based approaches requires cultural change, training, and updating of substantial documentation.

8.2. Data Integrity Considerations

Contemporary cleaning validation programs must address data integrity requirements applicable to all GMP documentation. Regulatory agencies have increased scrutiny of data integrity in recent years, with cleaning validation documentation subject to the same expectations as other quality records [40].

ALCOA+ principles (Attributable, Legible, Contemporaneous, Original, Accurate, plus Complete, Consistent, Enduring, Available) apply to cleaning validation records including: validation protocols and reports, analytical data and chromatograms, equipment logs, and training records. Electronic systems used for data acquisition, processing, or storage must be validated and equipped with appropriate access controls and audit trails [41].

8.3. Continuous Process Verification and Lifecycle Management

Risk-based cleaning validation increasingly incorporates concepts from continuous process verification, moving beyond initial validation to ongoing demonstration of cleaning process capability [42]. This approach includes:

- **Statistical process monitoring:** Application of control charts and capability indices to ongoing cleaning verification data.
- **Trend analysis:** Regular review of cleaning data for trends that might indicate process drift or developing problems.
- **Periodic revalidation:** Risk-based determination of revalidation frequency based on process performance history.
- **Knowledge management:** Systematic capture and application of cleaning process knowledge to improve performance over time.

8.4. Future Trends

Several emerging trends are likely to influence cleaning validation practice in coming years:

- **Predictive modeling:** Application of mechanistic and empirical models to predict cleaning performance and optimize cleaning procedures [43].
- **Continuous manufacturing:** Cleaning validation approaches for continuous manufacturing processes require adaptation from batch-based paradigms.
- **Advanced analytics:** Application of multivariate analysis, machine learning, and artificial intelligence to cleaning data interpretation and process optimization.
- **Sustainability:** Increasing attention to environmental impact of cleaning processes, including water and chemical consumption, driving efficiency improvements.
- **Harmonized guidance:** Continued regulatory convergence may yield more unified global expectations, reducing complexity for multinational manufacturers.

9. Conclusion

The evolution of cleaning validation from prescriptive, arbitrary criteria to risk-based, scientifically justified approaches represents a significant advancement in pharmaceutical quality systems. This transformation, driven by regulatory

developments including the seminal EMA 2014 guideline on health-based exposure limits and supported by ICH quality management frameworks, has placed cleaning validation on a sound scientific foundation.

Health-based exposure limits, derived through rigorous toxicological assessment, provide acceptance criteria that are inherently more protective for highly potent compounds while avoiding disproportionate burden for lower-risk substances. The integration of quality risk management tools including FMEA and HACCP enables systematic identification and control of risks, directing resources toward the most significant hazards.

Implementation of risk-based cleaning validation requires investment in toxicological expertise, analytical capabilities, and organizational change management. The challenges are significant but surmountable, and the benefits in terms of patient safety, regulatory compliance, and resource efficiency justify the transition.

As the pharmaceutical industry continues to evolve, with increasing prevalence of potent compounds, biological products, and complex manufacturing configurations, risk-based cleaning validation provides a flexible, scientifically grounded framework capable of addressing emerging challenges. Continued regulatory harmonization and development of supporting standards will further facilitate implementation.

The fundamental objective of cleaning validation—protection of patient safety through prevention of cross-contamination—remains unchanged. What has evolved is the scientific sophistication with which that objective is achieved, representing a maturation of pharmaceutical quality practices fully consistent with the risk-based, science-based quality paradigm embodied in contemporary regulatory expectations.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Authorship contribution statement

- **Birju Patel:** Conceptualization, Methodology, Writing- Original Draft, Writing - Review & Editing, Supervision.
- **Nageswara Pacha:** Writing - Original Draft, Writing – Review & Editing.
- **Jayminkumar Patel:** Writing – Original Draft, Writing - Review & Editing.
- **Ryan Le:** Writing -Review & Editing.
- **Abhishek Singh:** Writing - Review & Editing.

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