IntuitionLabs

INTUITIONLABS / RESEARCH & PRACTICAL GUIDANCE

Pharma Cleaning Validation: HBEL, PDE & Lifecycle Approach

> Build practical AI for pharma and biotech with IntuitionLabs. We help life-science teams turn complex information and workflows into useful software, governed knowledge systems and AI tools.

Published by IntuitionLabs · 2026-05-17 · cleaning validation · hbel · pde calculation · maco calculation · lifecycle approach · validation software · pharmaceutical manufacturing · cross contamination · gmp

Original article: https://intuitionlabs.ai/articles/pharma-cleaning-validation-hbel-pde-lifecycle



In this article

1. Cleaning Validation in Pharma 2026: Health-Based Exposure Limits (HBEL/PDE), the Lifecycle Approach & Validation Software
2. 1. Introduction and Background
3. 2.Health-Based Exposure Limits (HBELs/PDE/ADE)
4. 3. The Lifecycle Approach to Cleaning Validation
5. 4. Analytical Methods and Acceptance Criteria
6. 5. Cleaning Validation Software and Digitalization
7. 6. Case Studies and Real-World Examples
8. 7. Discussion: Implications and Future Directions
9. 8. Conclusion

Cleaning Validation in Pharma 2026: Health-Based Exposure Limits (HBEL/PDE), the Lifecycle Approach & Validation Software

Executive Summary. Cleaning validation is a critical component of pharmaceutical quality systems, ensuring that manufacturing equipment is free of residues that could compromise product safety or quality. In recent years the industry has shifted from simple acceptance limits (e.g. “10 ppm” rules) to *health-based exposure limits* (HBELs), such as the Permitted Daily Exposure (PDE) or Acceptable Daily Exposure (ADE), for setting residue limits. These approaches, endorsed by regulators and industry guidelines, rely on toxicological evaluations of APIs and cleaning agents to derive safe carryover limits. Simultaneously, the notion of a **lifecycle approach**—originating from process validation guidance—has become integral to cleaning validation. Under a lifecycle model, cleaning procedures are **designed**, **validated**, and then **continuously verified** through monitoring, change control, and risk management, rather than treated as one-off projects. In practice this means emphasizing cleaning process development (e.g. lab trials, worst-case studies) and ongoing metrics (e.g. trending, periodic re-assessments) in line with ICH Q10 and FDA guidance.

Digital tools are increasingly applied to cleaning validation: specialized software can automate tasks such as Maximum Allowable Carryover (MACO) and PDE calculations, protocol generation, data tracking, and audit-ready documentation. Industry surveys indicate that adoption of digital validation systems is rising – for example, a 2024 survey found ~30% of companies already use such systems for cleaning validation, with many more planning to digitize in the next 1–2 years (kneat.com). Case studies—from greenfield sterile plants to large pharma sites leveraging enterprise validation platforms—illustrate benefits of a lifecycle approach (e.g. proactive design, built-in risk analysis) and digital solutions (e.g. reduced cycle times, centralized data). For instance, Kneat reports that MSD (Merck Sharp & Dohme) digitized seven validation processes globally (the validation types are not specified) and, according to the vendor, reduced cycle times by 50% (kneat.com).

This report provides an in-depth analysis of cleaning validation in 2026, covering: the regulatory and historical context; the rationale and methodology of HBEL/PDE-based limits (with toxicology and calculation details); the lifecycle-based cleaning validation paradigm; analytical and statistical methods for cleaning verification; the role of risk management throughout; examples and case studies; and the emerging role of software and data analytics. Each topic is supported by data, citations from guidelines, industry literature, and expert sources. The implications for future practice – including further digitization, continual improvements in risk modeling, and alignment with advanced manufacturing (e.g. Pharma 4.0) – are discussed. This comprehensive report aims to equip quality and compliance professionals with the latest understanding and tools for cleaning validation.

1. Introduction and Background

1.1 The Purpose of Cleaning Validation. In pharmaceutical manufacturing, equipment often processes multiple products or batches. Without effective cleaning and validation, residual amounts of one product or its cleaning agents can carry over and contaminate subsequent batches, posing risks to patient safety and product quality (www.pharmtech.com) (manuals.plus). Cleaning validation is the documented evidence that a cleaning procedure consistently removes residues to defined acceptance criteria. As Wayne Goodwin (Biovectra) remarks, regulators expect that manufacturers "show that [the] cleaning acceptance criteria are appropriate" and backed by analytical validation (www.pharmtech.com). In practice, cleaning validation encompasses designing and testing cleaning procedures, sampling for residuals (e.g. swabs, rinses), analyzing samples, and setting limits to ensure safety. It is mandated by Good Manufacturing Practice (GMP) regulations worldwide (FDA, EU, WHO, PIC/S, etc.) and is part of regulatory inspections. For example, the EU GMP Annex 15 chapter on cleaning validation explicitly requires cleaning to be validated on *"all product contact equipment"* and that carryover limits be justified by toxicological evaluation (manuals.plus). Similarly, FDA's 1993 inspection guide, Validation of Cleaning Processes (7/93), and WHO/PIC/S guidelines emphasize scientific data showing that cleaning is effective. In short, *"the primary purpose of all cleaning validation activities…is protecting patient safety and product quality,"* a point stressed by industry and regulators alike (www.ecolab.com).

1.2 Historical Context and Guidelines. Early approaches to cleaning validation (1990s-2000s) often relied on fixed formulae or rules-of-thumb. Common methods included limits such as 10 ppm (0.001% w/w) of material on a surface, or 1/1000 of the maximum daily dose of the prior product allowed as residue (www.gmp-journal.com) (manuals.plus). These "deterministic" limits—often derived from engineering conventions or default pharmacopoeia—did not account for the specific toxicity of compounds. Over time, regulators and industry recognized the shortcomings of such rigid thresholds, especially for potent drugs, cytotoxics, or multi-step cleaning.

Starting in the early 2000s, risk-based and science-based approaches gained emphasis. ICH Q9 (2005) on Quality Risk Management encouraged systematically focusing on critical risks (e.g. cross-contamination in cleaning), and FDA's Process Validation (2011) guidance introduced the concept of process validation as a lifecycle. In parallel, regulatory agencies moved toward health-based limits: the EU's EMA/PIC S established HBEL/PDE guidelines (first EU draft 2012, final 2014) and WHO later endorsed analogous concepts (Acceptable Daily Exposure, ADE). EudraLex Annex 15 (version 4, 2015) explicitly states that cleaning limits

"should be based on a toxicological evaluation" (manuals.plus), signaling a firm departure from fixed ppm rules. The Annex even allows flexibility (for example, for biologics where toxicology is irrelevant) and directs use of worst-case criteria. The global trend culminated with specialized guidelines: EMA's CHMP/CVMP "HBEL Guideline" (2014, updated 2018) and its companion Q&As (2018), PIC/S's Aide-mémoires for inspections of cross-contamination risk (2018-2020), and WHO's 2021 *TRS 1033 Annex 2* on including HBELs in cleaning validation. These documents define PDE/ADE methodology and clarify how to apply HBELs to cleaning. Today in 2026, virtually all mature pharma markets expect toxicologically justified cleaning limits (PDE/ADE/TTC), and regulators explicitly support lifecycle/personalized approaches. As one industry expert notes, cleaning validation is now *"increasingly driven by scientific risk assessments"*, especially in multiproduct facilities (kneat.com).

1.3 Scope of this Report. This report systematically examines (a) the health-based exposure limit (HBEL) approach (PDE/ADE), (b) the lifecycle framework for cleaning validation, and (c) the role of specialized validation software and digital tools. We draw from regulatory guidance (EMA, FDA, WHO, PIC/S), industry publications (e.g. ECA ECA Academy, GMP Journal, Pharmaceutical Technology), and case studies. Section 2 details HBEL/PDE derivation, formulas, and regulatory use. Section 3 discusses the lifecycle approach to cleaning validation, contrasting it with traditional batch-based methods, and includes the role of risk management and change control. Section 4 covers analytical methods and acceptance criteria (swab/rinse sampling, method validation, and relevant metrics). Section 5 reviews the emergence of digital/automated tools: features of cleaning validation software, adoption trends, and examples. Empirical data (surveys, market analyses) and real-world examples are integrated to support the analysis. Section 6 presents case studies, and Section 7 explores implications and future directions (e.g. further digitization, continuous verification, integration with PAT/Pharma 4.0). Claims and assertions are grounded in literature and guidelines referenced throughout.

2.Health-Based Exposure Limits (HBELs/PDE/ADE)

2.1 Concept and Rationale.

Traditional cleaning limits (e.g. 10 ppm) did not account for drug potency or patient exposure. HBELs address this by tying limits to human toxicology. A **Permitted Daily Exposure (PDE)** is defined as *"a specific dose … that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime"* (www.pharmacalculation.com). Essentially, PDE (or the essentially equivalent Acceptable Daily Exposure, ADE, as used by WHO/US) is the largest daily intake of residue that poses no significant risk. PDE is expressed in mg/day (for a standard 50 kg person). By deriving limits from toxicological data, one ensures that even if a patient were to take the next product at its full daily dose, any carryover residue would contribute negligibly to risk.

Regulatory Context – Safety Limits. EMA's guideline explicitly frames PDE as an HBEL: *"Health-based limits through the derivation of a safe threshold value should be employed to identify the risks posed"*, with PDE or TTC cited as examples (pdf4pro.com). The EMA/CVMP guideline (2014/18) and PIC/S (2019) both emphasize PDE for cross-contamination risk. WHO's *TRS 1033 Annex 2* (2021) similarly endorses using HBELs in cleaning. These documents make clear: for each product residue the next patient might encounter, one must establish an HBEL.

Once a PDE (or ADE) is set for a substance, it is used to calculate the **Maximum Allowable Carryover (MACO)** on equipment. MACO (often expressed as mg of residue) defines how much drug from Product A may remain on equipment so that when Product B is made, patient exposure remains below PDE. (Section 5 discusses MACO calculation in detail.) In short, health-based cleaning validation ensures “no carryover of harmful active pharmaceutical ingredients” beyond PDE (www.leucine.io), directly protecting patient safety.

2.2 PDE Derivation and Formula.

The standard PDE calculation (following the approach in ICH Q3C Appendix 3) is:

> **PDE = (NOAEL × 50 kg) / ($F_1 \times F_2 \times F_3 \times F_4 \times F_5$)**,

where NOAEL is the no-observed-adverse-effect level (mg/kg/day) from animal studies for the critical toxicological effect (www.pharmacalculation.com). Each F-factor (≥1) accounts for specific uncertainties: interspecies extrapolation (F_1), human variability (F_2), short-duration studies (F_3), severe toxicity (F_4), and extrapolation when only a LOAEL (lowest-observed-adverse-effect level) is available (F_5). Typical default values are given in guidance and industry sources (www.pharmacalculation.com). Table 1 summarizes these adjustment factors:

Factor	Description	Typical Value(s)
F_1	Interspecies extrapolation (comparative surface area:body weight)	5 (rat), 12 (mouse), 2 (dog), 2.5 (rabbit), 3 (monkey), 10 (other animals)
F_2	Variability between individuals	10
F_3	Short-term exposure (study duration)	1 (studies of at least half a lifetime), 2 (6-month rodent study), 5 (3-month rodent study), 10 (shorter studies)
F_4	Severity factor (carcinogenicity, genotoxicity, neuro/teratogenicity) (www.pharmacalculation.com)	1 (none) up to 10 (if effect is severe)
F_5	Use of LOAEL instead of NOAEL (www.pharmacalculation.com)	up to 10 (if no NOAEL exists)

> *Table 1. Factors in PDE calculation (per EMA and ICH guidelines (www.pharmacalculation.com)). In practice, one identifies the lowest NOAEL (in mg/kg/day) for the critical effect, multiplies by a standard 50-kg body weight, then divides by the product of F_1–F_5. Where only a LOAEL is available, F_5 can be set (often =10) to compensate below-NOAEL gaps (www.pharmacalculation.com). If data are insufficient for any factor, conservative worst-case values are used (as noted above).*

In practice, thorough literature and sponsor data review (as outlined in A3P guidelines (www.a3p.org)) is conducted to identify key endpoints and justify factors. Notably, modern PDE derivation is a *structured toxicological evaluation*: a “PDE Monograph” is recommended, containing data collection and evaluation (Appendices, regulatory reports, etc.) (www.a3p.org). The result is a human-equivalent daily dose in mg/day that is deemed safe. For highly potent molecules (e.g. oncology drugs), or in contract manufacturing, PDE values can be particularly critical for cleaning risk assessment.

2.3 From PDE to Cleaning Limits (MACO).

Once PDE (in mg/day) is established for a residue (typically the outgoing product on equipment), it is translated into a limit on surfaces via MACO. A common form of the MACO (mg residue on equipment) formula is:

> **MACO = (PDE × Minimum Batch Size of next product) / (Maximum Daily Dose of next product)** (simplified form) (www.leucine.io).

This essentially scales the allowable carryover mass so that even if a patient takes the full daily dose of Product B, the share coming from a relic residue of Product A is at or below the PDE. (Different variants exist, sometimes including surface area factors or additional safety factors.) For example, if PDE of Product A is 0.5 mg/day, the next product B's smallest batch is 500 kg and its maximum daily dose is 1000 mg, then:

> MACO = (0.5 mg/day × 500 000 g) / 1000 mg = 250 g (250,000 mg of A on the equipment) (www.leucine.io).

This number (in mg of residue) can be converted to a concentration by dividing by total equipment surface area. Notably, several software tools now automate these calculations and maintain audit trails (www.leucine.io) (www.pharmaspotter.com).

(As an industry example, Goodwin of Biovectra emphasizes exactly this logic: cleaning acceptance criteria typically include an ADE/PDE for the preceding product and factors such as shared surface area and swab recovery (www.pharmtech.com). This matches the conceptual balance shown above.)

2.4 Regulatory and Industry Guidance on HBEL.

Agencies now explicitly expect HBEL-based limits. In Europe, both the EMA guideline (EMA/CHMP/CVMP/169430/2012) and the PIC/S equivalent recommend generating health-based limits (PDE) for risk identification in shared facilities. The WHO's Annex 2 (TRS 1033, 2021) provides "points to consider" for using HBELs in cleaning. These guidelines uniformly state that PDE (or ADE/TDI/ADI) should be used "wherever possible" instead of arbitrary assumptions. For example, A3P (France) notes that PDEs *"are used by cleaning validation specialists to establish the MACO value"* and to decide on dedicating equipment (www.a3p.org). EudraLex Chapter 10.6 specifically declares: *"Limits for the carryover of product residues should be based on a toxicological evaluation."* The Annex requires any limit to be justified via risk assessment with references (manuals.plus).

WHO and EU guidelines also acknowledge that other toxicological thresholds (e.g. Threshold of Toxicological Concern, TTC) may be applied if PDE cannot be computed. For instance, the EMA guideline mentions using TTC as an example of a safe threshold (pdf4pro.com). (TTC is typically very conservative, e.g. 1.5 µg/day for genotoxic impurities, and is seldom needed if any toxicology is available.)

In contrast, countries or operations lacking toxicology data may default to older criteria. For example, an authority might insist on re-introducing a legacy 10 ppm criterion even if PDE values are available (www.gmp-journal.com). However, industry guidance clarifies that historical limits for existing products *can* be retained only as "alert" limits and should not override PDE limits if PDE is more restrictive (www.gmp-journal.com). Specifically, as one expert explains, *"for existing products, manufacturer's historically used cleaning limits…*

can be considered as alert limits, provided they provide sufficient assurance that excursions above the HBEL will be prevented." (www.gmp-journal.com). In practice, this means companies often keep old limits as early warning, but design cleaning controls to meet HBEL-based MACOs.

2.5 Data and Tools for HBEL Setting.

Establishing a PDE requires gathering all relevant toxicology and pharmacology. Published guidelines and Q&A emphasize comprehensive literature searches, selection of critical endpoints, and justification of F-factors (www.gmp-publishing.com). Inspectors look for documented PDE assessments signed by qualified experts (CVs included) with full data sources (www.gmp-publishing.com). Figure 1 (below) illustrates a portion of what an examiner might expect on a PDE report's cover page (illustrative).

(www.pharmtech.com) (www.gmp-publishing.com)

Figure 1. Illustrative PDE assessment summary, showing substance identification, toxicological data sources and the selected PDE.

Several commercial and public tools assist PDE derivation. Some companies apply software that automates PDE calculations (often requiring user input for data and factors). Online calculators (e.g. pharmacalculation.com) also illustrate the formula and factors (www.pharmacalculation.com), helping analysts check their work.

3. The Lifecycle Approach to Cleaning Validation

3.1 From One-Time Validation to Continuous Control.

Traditional cleaning validation treated each product or campaign as a one-time event: one conducts a set of cleaning trials, demonstrates acceptable carryover, and then the procedure is "validated." Thereafter, revalidation might occur only if major changes happen. In contrast, a *lifecycle* approach embeds cleaning validation into the ongoing quality system. Inspired by FDA's process validation guidance (2011) and the ICH Q8/Q9/Q10 quality-by-design paradigm, this model envisions continuous verification of cleaning effectiveness, not a static snapshot. As Thomas Peither (GMP-Verlag) notes: **"The life cycle approach to cleaning validation simply means that control of cleaning effectiveness must be maintained on an ongoing basis"** (www.gmp-publishing.com). It involves three main phases (www.gmp-publishing.com) (ispe.org):

- **Design (or Development) Phase:** Establishing and optimizing the cleaning process before full-scale validation. This includes defining critical cleaning parameters (e.g. detergents, time, temperatures), conducting lab or pilot studies on cleanability, performing worst-case studies, and mapping out cleaning protocols. If "Quality by Design" is applied, a control strategy with built-in monitoring is established in advance (www.gmp-publishing.com). Robust design gives a stronger basis for the later validation and verification work. For example, the ISPE topical products article discusses using lab testing, equipment design review, and risk assessment to understand and design an effective cleaning process, thereby reducing validation workload (ispe.org).

- **Qualification (Validation) Phase:** Collecting data to demonstrate the cleaning process works under actual conditions (often on a defined number of full-size batches). This includes detailed cleaning validation protocols (linked to the master plan), performing swab/rinse sampling according to the plan, and analyzing to show results within limits. Importantly, this phase should include "challenge" or worst-case testing (e.g. using soils, placing the highest-risk equipment/locations, testing extended hold-times) to ensure robustness. As one source states, *"data must then be collected to prove the process reliability of the cleaning,"* possibly under unfavourable conditions (www.gmp-publishing.com).
- **Continued Verification (Monitoring) Phase:** After qualification, the focus shifts to ongoing oversight. This may involve routine monitoring (e.g. photometric tests, TOC, periodic swabs) of the cleaning process, trending of residue results, investigation of excursions, and periodic re-assessment when process or product changes occur. A key idea is that cleaning performance is continuously assured through in-process controls and quality records, rather than only through a special re-validation run. As Peither emphasizes, *"this control system…continuously provides data on the effectiveness of the cleaning process"* (www.gmp-publishing.com). In practice this can include statistical process control of swab results, annual reviews of cleaning data, or integration of cleaning checks into line clearance/Batch Release processes.

Figure 2 (below) illustrates the cleaning validation lifecycle model, adapted from industry sources (www.gmp-publishing.com) (ispe.org). Each stage flows into the next, linking process understanding, validation evidence, and surveillance.

(ispe.org) (www.gmp-publishing.com)

【Figure 2. Lifecycle model for cleaning validation – (1) Design/development of cleaning (lab tests, mapping, risk assessment), (2) Qualification (validation trials, batch sampling), (3) Continued Verification (monitoring, trending, revalidation). Source: ISPE/pharmeng and GMP-Logfile adaptations (www.gmp-publishing.com).

3.2 Risk Management in Cleaning.

Risk management is integral to the lifecycle approach. At every stage, cleaning processes should be designed and controlled based on risk to product patients. Early in the development phase, risk assessments identify which equipment, product/cleaner combinations, and parameters are critical. For instance, regulators point out that risk assessments are needed to justify selected cleaning limits and the number of validation runs (www.ecolab.com). Tools like HACCP-style hazard analyses or FMEA can be applied to cleaning (e.g. identifying worst-case active ingredients, cleaning agents, or equipment features). The EMA guideline on HBEL and PIC/S documents stress focusing on worst-case exposures. Annex 15 (§10.5) explicitly requires identifying variable factors (operators, rinse times, etc.) and, when found, using worst-case conditions in validation studies (manuals.plus). Ecolab notes that Annex 15 and ASTM E3106 (the cleaning standard) both mandate risk-based planning (e.g. grouping equipment and rationalizing swab locations) (www.ecolab.com).

A well-known example of risk-tiering is "worst-case product" or "worst-case equipment" selection. When a site makes many products, one product deemed hardest to clean (e.g. most potent, least soluble) may be chosen as the worst-case #1. The cleaning process is then validated primarily using that product, with the idea that if the process controls that one, it controls all others. Annex 15 §10.10 requires supporting any worst-case

choice with scientific rationale using criteria like solubility, cleanability, toxicity, and potency (manuals.plus). Similarly, equipment can be grouped by similarity and one representative cleaned on validation runs (with justification). These risk-based strategies minimize effort while still covering the key hazards.

As products or processes change, change control and periodic re-assessment are crucial. For example, if a new highly potent product is introduced into a facility, a risk assessment may mandate re-validation of existing cleaning processes to ensure the new worst-case is covered (www.gmp-journal.com). If cleaning procedures or detergents are modified, the cleaning lifecycle calls for verifying/process re-qualification. The current regulatory mindset views cleaning validation as a living program – hence the term “continued verification” – rather than a one-time checkbox (www.gmp-publishing.com) (manuals.plus).

3.3 Implementation of Lifecycle Cleaning Validation.

In practical terms, a lifecycle approach means cleaning validation programs are integrated with the overall quality system (QMS). Key elements include:

- **Cleaning Validation Master Planning.** A documented plan (often part of the Process Validation Master Plan or separate) outlining equipment, processes, parameters, and responsibilities for cleaning validation, aligned with product lifecycles.
- **Process Design and Method Development.** Activities to investigate cleaning (lab studies, swab method development, worst-case studies) occur early. This might include design-of-experiments (DoE) to optimize cleaning steps, or formal cleaning risk assessments (e.g. using prior product toxicity, cleaning agent capability, etc.).
- **Cleaning Procedure Qualification and Validation.** Formal protocols are executed on equipment (CIP, COP, or manual cleaning) with defined acceptance criteria (chemical and microbial). Protocols specify sampling locations (see below), actions for titer fails, etc. PDA Technical Report No. 29 is cited for a typical swab recovery of 70% or more to qualify a method, but there are no explicit regulatory requirements regarding chemical swab recovery rate (www.gmp-journal.com).
- **Ongoing Monitoring and Trending.** This can include routine environmental or end-of-clean sampling, control charts of residue results, periodic inspections, and linkages to equipment cleaning logs. Software and continuous data capture can facilitate this (see Section 5).
- **Periodic Review and Revalidation.** At set intervals or upon changes, the cleanliness history and any deviations are reviewed. If trends worsen or new risks emerge, corrective actions or additional validation runs may be needed. Inspectors expect readiness for such review (e.g. German GMP inspectorate checklist calls for up-to-date health risk assessments and material lists (www.gmp-publishing.com)).

In sum, the lifecycle approach aligns cleaning validation with modern quality paradigms: it is proactive (built-in during process design), comprehensive (covers all sources of variability), and continuous (monitored and updated). Thomas Peither summarizes: “This type of continuous verification does not end with revalidation of individual batches, but requires a control system that continuously provides data on cleaning effectiveness” (www.gmp-publishing.com).

4. Analytical Methods and Acceptance Criteria

4.1 Sampling and Analysis.

Central to cleaning validation are methods to detect residuals on equipment surfaces. Two primary sampling techniques are used： (www.gmp-journal.com):

- **Surface swabbing/wiping**: A defined surface area is wiped with a solvent/moistened swab, which is then analyzed (e.g. by HPLC, UV, TOC, microbiological culture). Swabs are needed for irregular or rough surfaces, corners, filters, or when equipment cannot be rinsed.
- **Rinse sampling**: A final rinse or drainage collected at the end of cleaning, representing the entire wetted volume. Rinse samples are easier for accessible pipe networks or tanks. However, they may dilute localized residues.

The choice of method depends on equipment design and feasibility. Annex 15 §10.12 allows swab and/or rinse (or other means) but requires justification of locations and demonstration of adequate recovery (manuals.plus). For validation, multiple sample points are typically taken (e.g. several spots for a tank), with each result required to meet the limit. Importantly, method validation is required: recovery must be demonstrated for the sampled product-contact materials; Annex 15 §10.12 sets no numeric criterion, and the ≥70% figure sometimes cited is an industry convention (e.g. PDA TR 29) rather than a regulatory requirement (www.gmp-journal.com).

Another test sometimes used is a **visual cleanliness check**. Annex 15 allows visual inspection as part of criteria (manuals.plus) but warns it cannot be the sole criterion. A study may, however, determine the lowest level of residue visually detectable and use that as a baseline. No formal regulatory % threshold exists for visual; it is only an “alert” or supporting measure.

For analytical chemistry, typical methods include HPLC/UV for API residues and TOC for total organic content (as a surrogate) (www.pharmtech.com). Microbiological testing (e.g. bioburden swabs, endotoxin tests) is also required for aseptic/sterile processes (www.gmp-journal.com). It is standard practice to validate every analytical method (specificity, sensitivity, etc.) against the residue acceptance limit (RAL). Shailesh Vengurlekar of LGM Pharma states: “The method may be considered valid for any RAL within the validated RAL recovery range” (www.pharmtech.com). Goodwin further notes methods must have adequate LOD/LOQ and selectivity; if the standard method (e.g. HPLC with methanol) is incompatible with a facility, an alternate must be found (www.pharmtech.com). Data integrity is emphasized: regulators will review method validation reports and cleaning data closely (www.pharmtech.com) (kneat.com).

4.2 Acceptance Criteria.

Chemical residues. For each residue (API or cleaning agent), acceptance criteria are typically set as concentration per surface area or as % carryover (relative to some reference). In a HBEL approach, one first calculates an absolute mass limit (MACO in mg) as described above. Then on each unit area or swab area, a corresponding limit (mg/cm² or ng/cm²) is derived. In some cases an absolute total limit is used (e.g. whole

surface). The actual number depends on surface area and batch size as shown in the MACO formula. For example, if MACO on a 100 m² (1e6 cm²) equipment is 250,000 mg, then the surface limit is 0.25 mg/cm² (250,000 mg/1e6 cm²) for each swab.

Annex 15 requires that limits consider *"the potential cumulative effect of multiple items of equipment in the process train"* (manuals.plus) – i.e. carryover down-line can accumulate. Thus, some companies allocate partial limits per piece or include additional safety margin. For cleaning agents (detergents, disinfectants), separate limits must also be defined, ensuring surfactants or solvents left behind are at acceptable levels (manuals.plus). If chemicals cannot be measured directly, Annex 15 allows using surrogates like total organic carbon (TOC) or conductivity as indicators (manuals.plus).

Microbial/endotoxin criteria (if relevant). In sterile environments (filling, isolators), cleaning validation also addresses microbial contamination. Microbial hold times need to be kept distinct: clean hold time (CHT) testing is first performed before sterilization, whereas sterile hold time (SHT) is linked to sterilization validation, aseptic processing and media fills rather than to cleaning validation (www.gmp-journal.com). Annex 15 §10.7 also requires considering the risk of microbial and endotoxin contamination when developing the cleaning protocol (manuals.plus), especially in water-sensitive processes.

Statistical considerations. In large validation studies, statistical tools are occasionally applied. For example, to ensure swabs are evenly collected, one may compute the overall carryover (MACO) and compare to PDE rather than each swab individually. However, inspectors caution against simply averaging swabs: if one swab fails, it indicates a problem and should be investigated (www.gmp-journal.com). In practice, the worst swab value is typically compared to the criterion. Fewer standard tools like ANOVA are used, but statistical process control charts are sometimes used in continued verification to track cleaning performance over time.

5. Cleaning Validation Software and Digitalization

5.1 Overview of Digital Tools.

With the push toward digitization and Industry 4.0, numerous software solutions have emerged to support cleaning validation. These tools range from specialized cleaning validation platforms to modules within larger MES/LIMS systems. They typically provide features such as:

- **Residue limit calculations (MACO)** – fully automated computation of cleaning limits (dose-based or PDE/ADE-based) given inputs of batch size, PDE values, safety factors, etc (www.pharmaspotter.com). Some tools include built-in toxicological databases or calculation engines.
- **Cleaning protocol and data management** – digital templates for cleaning validation protocols, checklists for swab locations and methods, electronic execution logs, and audit trails for documentation.
- **Sampling scheduling and integration** – coordination of swab/rinse sampling plans, logging of sample details, and often electronic interface to lab systems (LIMS) for tracking analytical results (www.pharmaspotter.com).
- **GMP compliance and reporting** – features to ensure 21 CFR 11 Part 11 compliance (electronic signatures, audit trails), standardized report generation, and readily displayable checklists or charts for inspections.

- **Risk analysis and decision support** – some incorporate logic for worst-case identification, product grouping, or risk assessment scoring to guide "which product/equipment to validate" (e.g. grouping similar products, as per Ecolab's guidance (www.ecolab.com)).
- **Data trending and continuous monitoring** – dashboards for long-term trending of residue or bioburden results, alert thresholds, and linking cleaning performance to CAPA systems.

PharmaSpotter (an industry software directory) summarizes that cleaning validation software "manages the entire cleaning validation lifecycle": *tracking cleaning procedures by product/equipment, calculating acceptable residue limits, coordinating sampling and testing, and maintaining FDA-inspectable documentation* (www.pharmaspotter.com). In short, these platforms mirror the process steps of Sections 2–4. For example, modern systems explicitly support risk-based and HBEL approaches – "AI-driven cleaning validation software [that] streamlines … MACO calculations, residue limit assessments [and] automated worst-case evaluation" is now marketed by vendors to meet inspectors' expectations (leucine.ai) (www.leucine.io).

5.2 Market Trends and Adoption.

Manufacturers are increasingly moving from spreadsheets and paper binders to digital cleaning validation tools. The 2024 *State of Validation* survey (Kneat Solutions and associates) found that **30%** of organizations actively use a digital validation system for cleaning, with **18%** planning to implement one within a year and **38%** within 1–2 years (kneat.com). These figures reflect survey respondents' stated intentions rather than confirmed adoption. Companies cite benefits such as reduced manual effort, consistency across sites, and better audit readiness. Industry commentary highlights this shift: *"digital transformation automates data collection, reducing manual errors… companies are increasingly leveraging digital validation systems to streamline [cleaning validation] processes"* (kneat.com). Not surprisingly, specialized vendors have commercialized solutions: for instance, ValGenesis offers an integrated "iClean" module, and AmpleLogic, Leucine (CLEEN), eResiduePro, and others have cleaning-specific products. Many MES vendors (e.g. Körber's PAS-X Equipment Management) now include cleaning protocol tracking.

Case Example – Integrated Digital Platform. In March 2025, ValGenesis announced that a global pharma company had fully digitized its cleaning validation lifecycle using **iClean** (ValGenesis's cleaning module) (www.valgenesis.com). Previously the company relied on a mix of digital systems, with Stage 2 managed within the ValGenesis platform while Stages 1 (cleaning process design) and 3 (continuous monitoring) were handled separately, resulting in data silos; the company moved to a single system: design, qualification, and continued verification became seamless. Reportedly this eliminated data silos and ensured consistency: *"it is setting a new standard for efficiency, compliance, and operational excellence,"* claimed the vendor. (ValGenesis says the company plans to deploy iClean at all global manufacturing sites.) Such case studies underscore how digital tools can unify cleaning plans, automate risk assessments (worst-case calculations, MACO, etc.), and provide real-time compliance data.

5.3 Software Features and Best Practices.

Table 2 below summarizes typical features found in cleaning validation software, drawn from industry sources (www.pharmaspotter.com) (www.leucine.io). These illustrate how software addresses the tasks outlined in previous sections.

Feature	Description
Residue Limit Calculation	Automated MACO/MAC and carryover calculations using dose- or HBEL-based limits (www.leucine.io) (www.pharmaspotter.com). Can incorporate PDE/ADE values and safety factors.
Cleaning Protocol Management	Electronic templates and version control for cleaning validation SOPs and protocols. Coordinates execution steps and documentation (timestamps, sign-offs) (www.pharmaspotter.com).
Sampling Coordination	Plan and log swab or rinse locations. Track sample chain-of-custody. Interface with LIMS to import analytical results for each sample (www.pharmaspotter.com).
Analytics Integration	Integration with laboratory information systems (LIMS) or databases for residue/drug assay results. Allows immediate validation vs. criteria when results are entered.
Compliance Reporting	Generates audit-ready reports and dashboards. Ensures full ALCOA++ data integrity (traceability, audit trails) for all entries. 21 CFR 11 compliance features.
Risk-Based Tools	Support for selecting worst-case products and equipment, using HBEL/PDE or pre-established criteria. Some systems provide risk scores or grouping logic (per ASTM E3106 recommendations).
Continuous Monitoring	Trending charts of cleaning metrics (e.g. swab results over time), with alerting if trends approach limits. Some can manage visual inspection checklists and hold-time monitoring.

Table 2. Common features of cleaning validation software platforms (illustrative). Sources: vendor and industry descriptions (www.pharmaspotter.com) (www.leucine.io).

In practice, companies consider such features alongside quality needs. A typical desired capability is computerized MACO calculation with audit trail (www.pharmaspotter.com). Others emphasize seamless recall of product/formulation data or direct linkage to validated analytical methods. Given the regulatory focus on data integrity (see Section 4.1), software must enforce controls (e.g. only approved parameters can be changed, with rationale logged) and support “electronic batch records” (eBMR) for cleaning.

5.4 Impact on Efficiency and Compliance.

Adopting specialized software has demonstrable efficiency effects. Vendors cite figures like “>98% effort reduction in MACO analysis” and “~60–90% reduction in documentation effort” on promotional material (e.g. AmpleLogic) – though these are vendor-claimed. Kneat, a validation-software vendor, reports that MSD (Merck Sharp & Dohme) digitized seven validation processes globally (the types are not specified) and reduced cycle times by 50% (kneat.com). These are vendor-reported figures rather than independent survey data. Similarly, automation of limit calculations and reporting frees QA personnel to focus on investigation and improvement rather than arithmetic.

Digital platforms also facilitate compliance: regulators routinely request to see cleaning data, trend charts, and justifications. Having instantaneous access to past cleaning runs and parameters (rather than searching paper logs) greatly aids audit readiness. According to industry sources, instant data access and elimination of manual data entry are major advantages (www.valgenesis.com) (kneat.com). For example, ValGenesis stated that its unified digital approach provides instant access to data for audits and inspections (www.valgenesis.com). In essence, while not yet universal, the integration of IT systems into cleaning validation is growing and aligns with broader quality digitalization trends.

6. Case Studies and Real-World Examples

6.1 Sterile Injectable Facility (Performance Validation).

One illustrative case is the cleaning validation of parts washers for a new injectable drugs site (Performance Validation case study, 2023) (perfval.com). For this injectable setup, reusable components (e.g. aseptic filling pistons, connectors) required qualification. PV engineers executed **42 full washer runs** on two parts washers, collecting both swab and rinse samples (perfval.com). Acceptance criteria were multi-tiered: visual cleanliness, final-rinse conductivity, swab TOC (for chemical residue), and swab bioburden (perfval.com). Key outcomes included:

- **Worst-Case Sampling:** Swabs targeted equipment that directly contacts APIs (e.g. scoops and injection needles) at predefined, risk-assessed locations, and rinse samples verified overall cleanliness (perfval.com). This risk-based approach focused sampling on the highest-risk surfaces.
- **Hold-Time Studies:** The validation included a 7-day dirty-hold test (dirty hold time, DHT) to mimic worst-case soiling; equipment had to be cleaned effectively after such hold. (The case study reports that this validated the ability to clean items left soiled for up to seven days, simulating worst-case residue (perfval.com).)
- **Troubleshooting & Improvements:** The case study reports issues surfaced during the runs: a failed bioburden swab traced to validation gowning that did not match production practice, and a scoop that did not dry until its load orientation was changed (perfval.com).

This case highlights several system-level points: (a) an extensive validation (42 test runs) is sometimes necessary to capture variability; (b) validation runs can uncover equipment design or SOP gaps that must be corrected, such as the alignment of validation gowning with production practice; (c) linkages between cleaning and aseptic processing, such as gowning, are important. The findings led to changes in equipment and procedures, illustrating the feedback a lifecycle approach is meant to capture.

6.2 Biotech Batch-to-Batch (Topical Products).

A published industry example (Hadziselimovic et al., 2023, *Pharmaceutical Engineering*) describes a lifecycle approach to cleaning validation at a multi-product site making topical products (the example concerns topical drug products, not biologics) (ispe.org). The site's roughly 300 products were narrowed to about 60 selected products during development and grouped into eight product families (A–H), based primarily on product chemistry. Laboratory testing started with the hardest-to-clean products and varied cleaning agent concentration, cleaning time and temperature, and a 125 L pilot unit supported scale-up to the production systems. The article organizes the work into the three lifecycle stages of design, qualification and continued verification, and describes the design-stage laboratory testing as providing a starting point for the critical cleaning parameters.

6.3 Digital Transformation (Merck / MSD).

Kneat's MSD (Merck Sharp & Dohme) case is notable for its scale. According to Kneat, MSD digitized seven validation processes globally, reducing cycle times by 50% and process steps by 46% (kneat.com). The source does not specify which validation types were digitized, so this result should not be read as specific to cleaning

validation; it is a vendor-reported illustration of the impact a digital workflow can have on validation work.

6.4 Industry Survey Data.

Broad surveys provide industry-wide context. Besides the *State of Validation* metric above, a PDA Letter article reviewed how cleaning and disinfection practices have evolved over 20 years (www.pda.org). Kneat's 2024 *State of Validation* cleaning-validation whitepaper reported that **78% of organizations outsource some of their validation activities**, with 32% outsourcing over a quarter of their validation efforts, driven by expertise and cost factors (kneat.com). These numbers indicate cleaning validation is recognized as specialized work requiring dedicated resources. These data suggest companies are leveraging external tools and services – including software – to manage the cleaning lifecycle.

7. Discussion: Implications and Future Directions

7.1 Evolving Regulatory Expectations.

Regulators continue to refine expectations on cleaning validation. Revision of standards reflects the lifecycle and risk-based paradigm. For instance, the EU's revised Annex 1 on sterile medicinal products (published in 2022 and in operation from 25 August 2023) is built around a Contamination Control Strategy, indirectly affecting cleaning practices. Agencies also assess documentation: the German GMP inspectorate's aide-mémoires (2023) specify detailed cleaning documentation that should be inspection-ready (PDE assessments, residue analyses, next-product lists, etc.) (www.gmp-publishing.com). ICH guidelines (Q9, Q10, Q12) all reinforce controlling processes through their lifecycle.

Concurrently, global harmonization of HBEL procedures is progressing. The EMA and PIC/S documents mean HBEL/PDE methodology is now widely used as the reference approach for toxicology-based limits. Some gaps remain, however: not all low-income regions have strict enforcement, and some smaller firms cling to legacy metrics. But overall, regulatory pushback to using PDE methods is unlikely. Instead, regulators may increasingly expect justification of HBEL derivations themselves (requiring qualified toxicologists or PBPK modeling). The trend may move toward more detailed toxicology review, including use of novel tools like (Q)SAR or computational models if animal data are scarce.

7.2 Industry 4.0 and Digital Quality.

The digital transformation in cleaning validation ties into broader manufacturing trends (Pharma 4.0). Facilities moving toward real-time monitoring may see cleaning validation integrate with sensing technologies. For example, in-situ analytical sensors (Raman, NIR) could one day monitor surfaces or rinse solutions during cleaning cycles, providing immediate pass/fail indications. Some sites now sample rinse water with at-line TOC or conductivity monitors. In the long term, "smart" cleaning systems might adjust cycles dynamically based on sensor feedback, further blurring lines between process control and validation, much as FDA envisioned for other processes.

Artificial intelligence and advanced analytics will play larger roles. Already, AI-powered software (e.g. AmpleLogic describes "AI-powered cleaning validation") promises to streamline workflows like worst-case analysis. Machine learning could help predict cleaning outcomes based on product/cleaner properties and past

data, optimizing protocols. Also, integration with plant-wide data: cleaning validation results might be correlated with batch quality data or environmental monitoring, enabling holistic contamination control strategy.

7.3 Training and Cultural Change.

Adopting a lifecycle, risk-based approach requires cultural shifts. Cleaning used to be seen as a chore; now it is a subject of rigorous scientific study. Organizations must ensure cross-functional understanding: operators, QA, production, and toxicologists need to collaborate more than in a legacy model. Training for analysts and engineers (e.g. on how to derive PDE) is more important. Some companies create specialized cleaning validation teams combining engineering and QA/QC experts.

Resistance can arise – for instance, a GMP Journal Q&A describes a case in which local authorities still insist that a solid-oral-dose site re-introduce the 10 ppm criterion even though PDE values are available for all of its products (www.gmp-journal.com). Education and evidence are key. Published case studies, internal retesting/monitoring, and relevant training modules (e.g. what is PDE and how it's justified) help stakeholders buy in. Professional organizations (PDA, Parenteral Drug Association; ISPE; ECA) actively offer training on these topics.

7.4 Sustainability and Resource Efficiency.

An emerging concern is sustainability. Cleaning typically uses large volumes of water, chemicals, and energy (heated CIP cycles). In response, companies are investing in "green cleaning" practices: optimized cleaning cycle design to minimize resources, reclamation of cleaning solutions, and more efficient cleanroom sterilants. While not the main focus of validation regulatory science, this theme appeared in recent industry reports "Sustainability is gaining importance…minimizing the use of paper, water, energy, and cleaning agents" (kneat.com). Digital validation systems themselves reduce paper and travel (e.g. virtual audits). Going forward, environmental impact may be factored into risk assessments – for example, selecting cleaning agents that are effective yet biodegradable, or programming CIP energy usage as a parameter to optimize alongside effectiveness.

7.5 Future Research and Tools.

Areas for further advancement include: robust methods for biologics cleaning (where traditional chemistry/TOC tests may be insufficient); better models for actual patient/worker exposure (refining PDE with pharmacokinetic modeling); and standardized databases of PDEs (some industry groups are exploring open-source HBEL libraries). Statistical methods from other industries (Design of Experiments, multivariate analysis) can further optimize cleaning.

In the software arena, interoperability will improve: integration between LIMS, MES, and cleaning modules will create unified lifecycle documentation (as MSD's case illustrates). Electronic Batch Records (eBMR) that include cleaning steps will become more common, enabling paperless audits. Artificial intelligence may automate routine QA tasks like reviewing cleaning batches for anomalies.

Regulations will likely continue to evolve but along these trends: more guidance on applying lifecycle principles (perhaps an FDA/SPC checklist for cleaning), greater emphasis on supply-chain contamination (e.g. consider drug residues in manufacturing water if relating to cleaning), and international convergence (more countries

formally adopting HBEL guidelines).

In summary, cleaning validation in 2026 is markedly different from 20 years ago. It is now a data-driven, risk-managed, and dynamically monitored part of pharmaceutical quality assurance. The combination of health-based toxicology limits, lifecycle thinking, and digital tools offers a higher assurance of patient safety and process efficiency. The challenge for industry is to integrate these elements into everyday practice, backed by the extensive guidance and examples now available in the literature.

8. Conclusion

Cleaning validation has become a model discipline for applying modern quality concepts (science-based limits, lifecycle management, digital integration) in pharmaceutical manufacturing. The shift to HBEL/PDE-based acceptance criteria grounds residue limits in toxicology and aligns expectations across global regulators. The lifecycle paradigm ensures that cleaning is not “validated and forgotten” but continuously controlled via risk assessment and monitoring. Validation software and analytics are emerging enablers, automating complex calculations and stitching together data.

Our review of guidelines, case studies, and industry sources shows that companies adopting these practices are positioned to benefit from streamlined validation projects and – crucially – strong assurance of cross-contamination control. Looking ahead, continued emphasis on patient safety and product quality will drive deeper implementation of HBEL strategies and life-cycle cleaning. We can expect further refinement of methods (analytical, statistical, and computational) and wider digitalization (e.g., cleaning data as part of “smart factory” systems). By 2026, cleaning validation will be dominated by these health-based, risk-managed, and automated approaches, making it more robust and efficient than ever.

Sources: Regulatory guidelines and training materials (EMA, FDA, PIC/S, WHO), industry publications (Pharmaceutical Technology, GMP Newsletters, ECA Academy, PDA technical reports), and software/vendor literature were consulted in preparing this report. Citations have been provided for all key statements above (www.pharmacalculation.com) (www.a3p.org) (www.pharmtech.com) (www.gmp-journal.com) (www.gmp-publishing.com) (manuals.plus) (www.gmp-publishing.com) (ispe.org) (www.ecolab.com) (www.pharmaspotter.com), among others, to ensure traceability of information. All figures and tables are synthesized from these sources as indicated.

Source links

Links cited in this article, in order of first appearance. Full addresses are provided for readers using extracted text.

1. https://kneat.com/article/cleaning-validation-trends
2. https://www.pharmtech.com/view/proving-it-s-clean-with-analytics
3. https://manuals.plus/m/1c3dbbbdf058fd2e0ef2da69192279e6e4bb13d3383bbd6fcb8a9da9b339c1cf
4. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-guides/validation-cleaning-processes-793
5. https://www.ecolab.com/articles/2023/10/designing-a-risk-based-cleaning-validation-process
6. https://www.gmp-journal.com/current-articles/details/cleaning-validation-q-a.html

7. https://www.pharmacalculation.com/2022/11/permitted-daily-exposure-calculation.html
8. https://pdf4pro.com/view/guideline-on-setting-health-based-exposure-limits-for-use-6feb29.html
9. https://www.leucine.io/cleaning-validation-blogs/maco-calculation-in-cleaning-validation-a-complete-guide
10. https://www.a3p.org/toxicological-approach-to-define-the-pde-for-your-cleaning-validation-process
11. https://www.pharmaspotter.com/solutions/cleaning-validation
12. https://www.gmp-publishing.com/blog/agency-expectations-on-pde-determination-and-pde-reports
13. https://www.gmp-publishing.com/content/en/gmp-news/gmp-newsletter/gmp-logfile-lead-article/d/1658/gmp-logfile-47-how-can-life-cycle-approac-be-applied-to-cleaning-validation
14. https://ispe.org/pharmaceutical-engineering/january-february-2023/life-cycle-approach-cleaning-topical-drug-products
15. https://leucine.ai/cleen
16. https://www.valgenesis.com/news/global-pharma-leader-digitizes-entire-cleaning-validation-lifecycle-with-valgenesis-iclean
17. https://perfval.com/case-study/cleaning-validation-injectable-manufacturing
18. https://www.pda.org/pda-letter-portal/home/full-article/the-evolution-of-cleaning-and-disinfection-practices-over-20-years

THE PUBLISHER

About IntuitionLabs

IntuitionLabs is an AI consulting, custom software development and data engineering firm serving pharmaceutical, biotechnology, medical-device and other life-science organizations. We work with clinical, regulatory, medical-affairs, commercial, quality and IT teams to connect technology decisions with the work people need to accomplish.

AI consulting and adoption

Our AI enablement services cover readiness assessments, use-case selection, governance and policies, team workshops, adoption measurement and ongoing advisory support. We help organizations structure the information layer behind AI: source material, context, permissions and maintained knowledge that make generated answers useful and reviewable. Private LLM inference and hosted AI options support teams evaluating how to operate AI with appropriate control over their data and infrastructure.

Software, data and life-science workflows

IntuitionLabs develops custom software for pharma and biotech, integrates enterprise systems, and builds data engineering and business intelligence solutions. Areas of focus include AI agents, regulatory research, medical writing, medical affairs, CMC information, competitive intelligence and clinical-document workflows. Our eTMF intelligence work includes cross-system reconciliation and inspection-readiness support.

Enterprise platforms and regulated delivery

We provide Veeva services, application support, managed services, integrations and custom applications, alongside enterprise content work involving platforms such as Egnyte. For regulated workflows, our services include GxP enablement, computer-system validation and software development addressing 21 CFR Part 11 requirements. The applicable controls, validation responsibilities and acceptance criteria are defined for each engagement.

Work with IntuitionLabs

Explore AI enablement, pharma and biotech software development, data engineering and BI, and Veeva services. Contact IntuitionLabs to discuss your workflow, information sources and implementation needs.

IntuitionLabs publishes educational research to help life-science teams make informed technology decisions. Coverage of a product or organization does not imply a client relationship, endorsement or partnership.

Website: https://intuitionlabs.ai

This article is educational. Verify consequential medical, legal, financial, regulatory and technical decisions with appropriate professionals and the cited primary sources. Company services are described separately from the article's research findings.