



**ECOLAB<sup>®</sup>**

# Biopharma Equipment Cleaning

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A practical guide to effective and  
validated equipment cleaning

GLOBAL EXPERTS IN  
CONTAMINATION CONTROL

# Introduction

Biopharma companies require validated cleaning cycles in order to ensure compliant manufacture. Efficiency and effectiveness are two critical elements of this.

This guide reframes key optimization opportunities into actionable steps—what to adjust, why it matters, and how teams can execute these improvements on the floor.

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# How to Speed Up Changeovers



To shorten changeovers, focus on **optimizing time in the areas that matter most: cycle engineering, residue removal efficiency, manual execution consistency, and documentation flow. By identifying, quantifying, and optimizing these variables, teams can deliberately reduce cleaning duration while maintaining predictable, validation-ready performance.**

## 1. Improve chemistry efficiency to reduce rinse time

- ▼ Select easy to rinse chemistries so rinse steps reach conductivity/TOC pre-determined acceptance criteria faster
- ▼ Use rinse performance as a diagnostic. If conductivity or TOC endpoints are slow to clear across repeated cycles, evaluate whether your detergent chemistry is leaving residual films that require extended rinsing
- ▼ Run side by side rinse time comparisons using conductivity trends to quantify improvement

## 2. Re engineer CIP phases using TTCF (time/temperature/concentration/flow)

- ▼ Look at each CIP step (pre rinse > wash > intermediate rinse > second wash > final rinse) and ask: "Is this step optimized based on cleaning process development data or maybe longer than it needs to be for the residues actually present in the system?"
- ▼ Start assessing wash steps based on actual residue removal behavior (based on cleaning process development studies), not fixed historical times
- ▼ Verify spray ball coverage so you aren't compensating with extra time for poor mechanical action

# How to Speed Up Changeovers



## 3. Introduce real time indicators of wash completion

- ▼ Use turbidity, COD analysis or conductivity breakpoints to determine when soil removal has plateaued

## 4. Reduce operator variability in manual steps

- ▼ For isolators, COP parts, or gaskets, document consistent cleaning motions, coverage patterns, cleaning agent concentration, temperature and pressure applied as applicable for the application
- ▼ Establish visual residue limits (VRL) and train operators on visual inspection properly to reduce re-cleaning activities
- ▼ Implement a robust training plan for operators executing manual cleaning operations to reduce and control variability

## 5. Digitize non-value-added changeover time

- ▼ Move from paper records to digital logbooks to eliminate end of cycle paperwork bottlenecks
- ▼ Auto record flow, temperature, time and concentration so operators don't manually transcribe them

### Outcomes

You shorten cleaning phases, compress rinse time, reduce re clean cycles, and eliminate documentation delays — shrinking changeover in a controlled, defensible way.

# How to Reduce Residue Risk



Residues are a common root cause of cleaning failures in multi-product biopharma operations. Unlike small molecule manufacturing, residues here are rarely simple or uniform; they often include proteins, cell debris, media components, and buffers that are difficult to see and harder to remove. These residues are often difficult to detect visually and require engineered, optimized cleaning strategies to remove reliably.

## 1. Start with a residue risk map of your equipment

- ▼ Use engineering drawings or walkdowns to mark **difficult to clean** areas:
  - Dead legs
  - Spray shadow zones
  - Threaded fittings, o rings, gasket seats
  - Impellers, baffles, shaft housings
  - Hose couplings and TC joints
- ▼ Make these locations mandatory part of routine sampling plans if they are identified as risk for the process, patient safety or product quality

## 2. Use science-based residue limit setting

- ▼ Establish residue acceptance limits using **science-based criteria** (e.g., toxicology, PDE, product potency, process risk). Overly low limits do not inherently increase quality and often extend cleaning cycles without additional patient or product protection
- ▼ Once limits are justified, break equipment into logical sections and calculate surface area for each to ensure realistic, proportional distribution of allowable residue
- ▼ Apply material-specific recovery factors (e.g., SS316L, PTFE, glass) to reflect **actual detectability**, not theoretical cleanliness
- ▼ Scale rinse volumes and cycle design based on both **surface area and limit rationale**, ensuring cleaning cycles are fit for purpose and do not unnecessarily constrain production capacity

## How to Reduce Residue Risk



### 3. Engineer cycles to remove residue where it actually accumulates

- ▶ Increase flow in low velocity areas that tend to trap residues
- ▶ Address spray shadow areas either with targeted manual cleaning or targeted nozzles
- ▶ Apply wash temperatures high enough to solubilize media/protein residues but within material compatibility limits
- ▶ For sticky or thermally sensitive soils, extend recirculation but shorten other phases accordingly

### 4. Prevent disinfectant inefficiency caused by detergent residue

- ▶ Ensure cleaning steps fully remove detergent residues prior to disinfection—cleaning agent ingredients can neutralize disinfection agents or reduce their contact effectiveness
- ▶ Include at least one final rinse that returns conductivity/pH to pre-defined acceptance criteria level

### 5. Trend your residue data to drive continuous improvement

- ▶ Plot TOC values, swab recoveries, and conductivity baselines across batches
- ▶ Identify patterns, e.g., certain products consistently load more residue, certain circuits clean less predictably
- ▶ Gain cleaning process understanding and use statistical tool to evaluate cycle parameters in real time proactively rather than waiting for deviations

## Outcomes

Residue hotspots become controlled instead of unpredictable. Failures decrease, re cleans drop, and downstream disinfection becomes more reliable.

# How to Strengthen Validation Readiness & Speed to Market



As Annex 1 (Manufacture of Sterile Medicinal Products) as well as Annex 15 (Qualification and Validation) reinforce the need for structured contamination control strategies, inspectors are increasingly looking for coherence: alignment between documented rationale, actual practice, and data.

Validation takes much longer when cleaning processes are inconsistent, sampling plans are ambiguous, and documentation is manual. In those circumstances the documentation efforts increase significantly. The goal is to make validation a confirmation of control.

## 1. Build sampling plans that reflect actual risk, not tradition

- ▼ Define specific, repeatable sampling (including swab) locations—use images, angles, and exact placement
- ▼ Pair swab points with logical rinse points to verify both direct product contact surface sampled and system-wide cleanliness
- ▼ Assign analytical methods based on residues and risk identification:
  - TOC for total organic load (total nitrogen (TN) to identify TOC/TN ratio) for protein/product identification
  - Conductivity/pH for ionic residues
  - Photometric methods for specific actives or excipients in case of higher risk situations

## 2. Structure your validation around realistic worst case logic

- ▼ Group products by cleanability and validate against residues that genuinely represent worst case, not just chronologically newest
- ▼ Clearly document the scientific rationale for the grouping (solubility, toxicity, potency, and others like stickiness, protein load, excipient behavior, etc.)
- ▼ Validate cycles at least optimal TTCF conditions to build defensible operating windows

# How to Strengthen Validation Readiness & Speed to Market



## 3. Use DHT and CHT strategically instead of reactively

- ▼ Identify if Dirty Hold Time (DHT) does has an impact on the cleaning process using cleaning process development studies. If DHT does not have an impact, then the time period might not need to be qualified
- ▼ If DHT is identified to have an impact on the cleaning process, validate Dirty Hold Time long enough to cover normal operational delays, not just idealized conditions
- ▼ Validate Clean Hold Time (CHT) under environmental conditions the equipment actually sees — humidity, room class, downtime duration
- ▼ Monitor DHT and CHT using real time data to display process safety and consistency including trend analysis, not guesswork

## 4. Digitize validation documentation to eliminate bottlenecks

- ▼ Use structured templates for worst case identification, cleaning validation protocols, sampling sheets, acceptance criteria identification, and result summaries
- ▼ Link analytical results (TOC, HPLC, conductivity) directly to protocol sections
- ▼ Automate change assessments, deviations, approvals, and data capture so validation doesn't stall waiting for paperwork
- ▼ Real time availability of all relevant data, change assessments and reports for inspections, reduce preparation work down to a minimum

## 5. Trend cleaning performance like a process

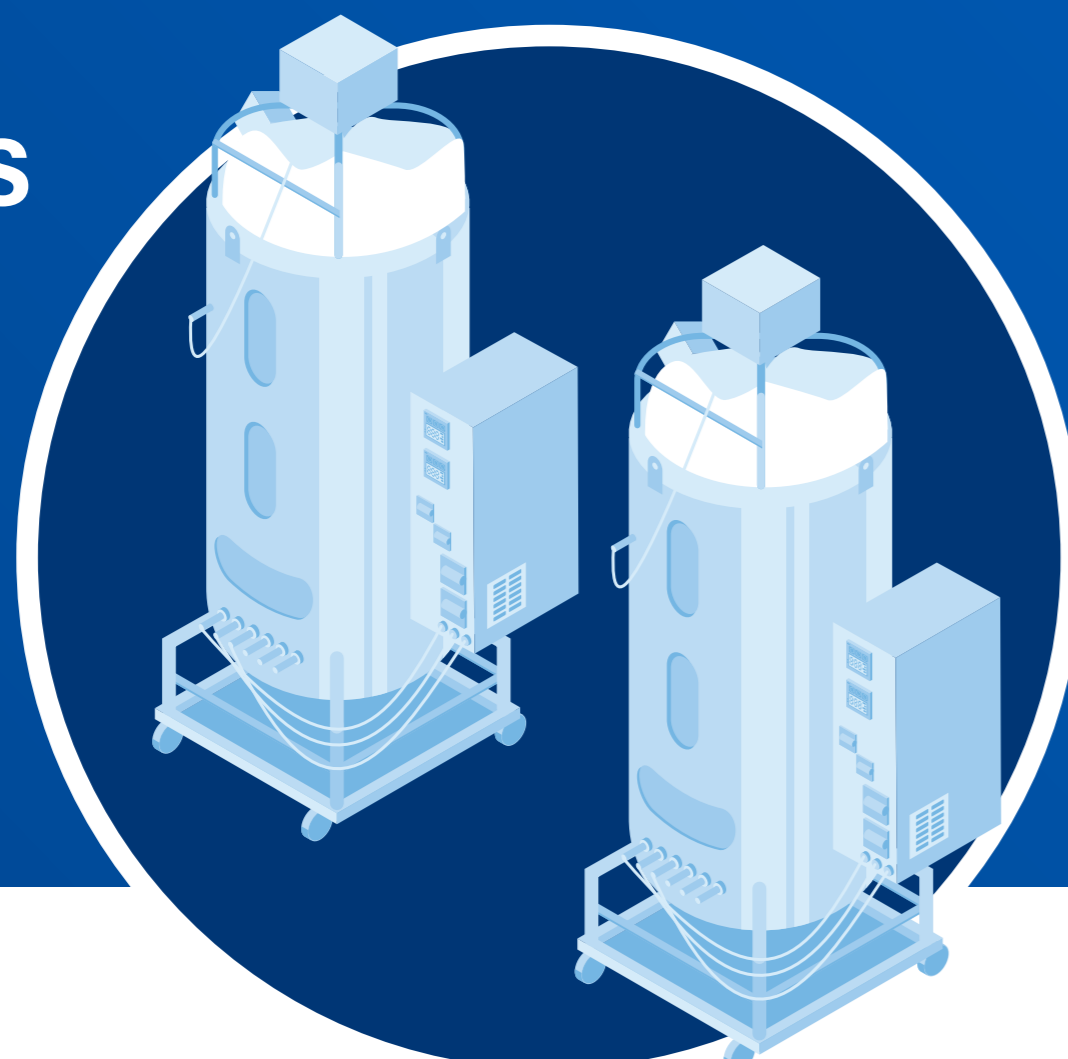
- ▼ Monitor whether cleaning performance is degrading or stabilizing as campaigns progress
- ▼ Identify circuits or steps where drift is occurring—flow loss, temperature undershoot, insufficient chemical concentration—and correct them before a re-validation is triggered

## Outcomes

Validation becomes predictable, documentation becomes easier, and inspection readiness becomes more engrained.

# How to Optimize Cleaning for Specific Equipment Types

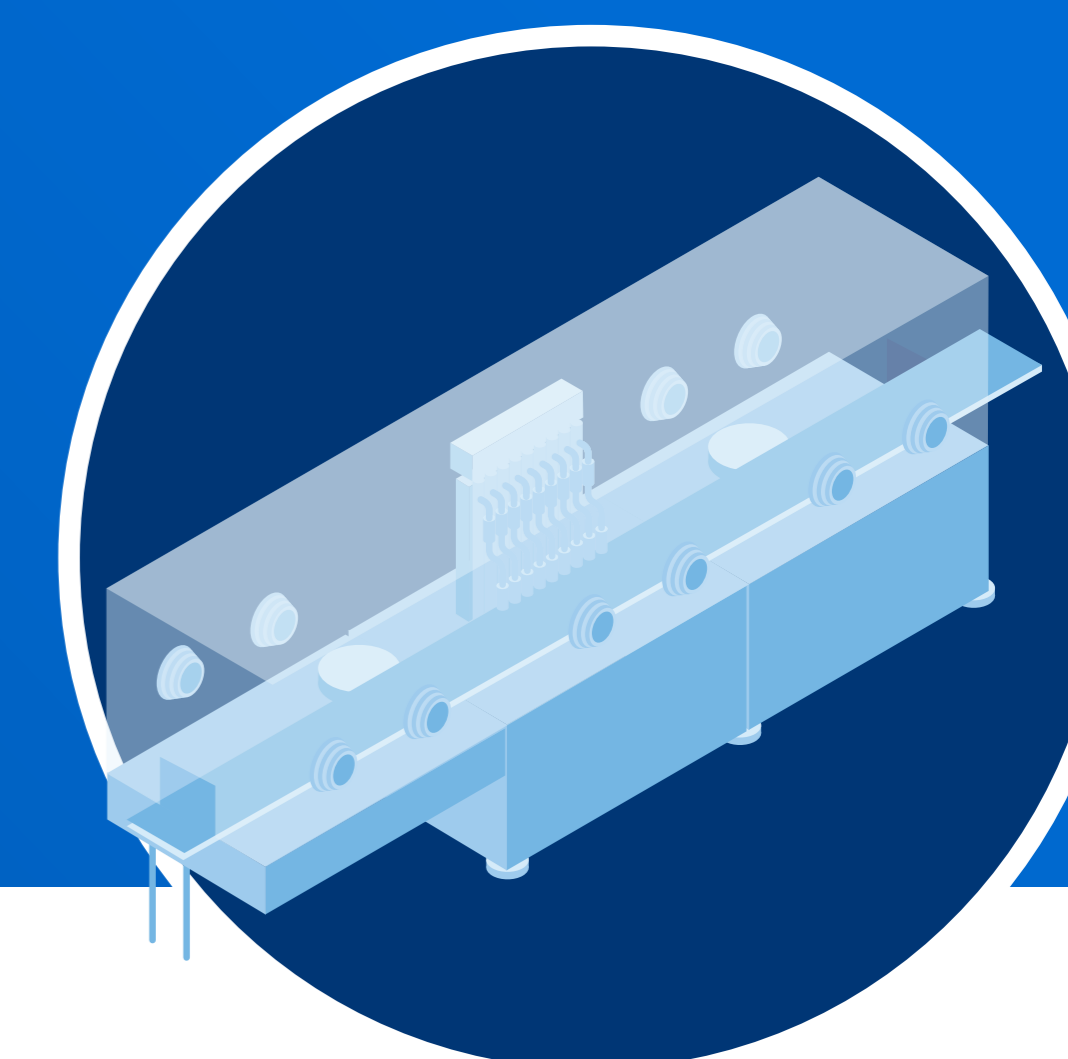
## Bioreactors



## Transfer Lines



## Isolators



### How to engineer a predictable, fast CIP

- Adjust CIP steps with the knowledge gained using cleaning process development studies—use, temperature profiles, concentration determination, flow rates or pressure measurement together with the time profile to display effective and consistent cleaning performance
- Use cleaning agent that match the residue type—high protein media often require specific pH and temperature bands for solubilization
- Validate CIP performance at normal operating conditions to define defensible operating conditions

### How to eliminate hidden failure points

- Operate cleaning activities at sufficient flow velocity to ensure turbulence throughout elbows, long runs, and hose sections
- Use pulsation or periodic flow reversal to disrupt early-stage biofilm formation. If biofilm does form, use sanitizers that are formulated to break down biofilms
- Treat connectors, hoses, and TC joints as high risk areas requiring clear sampling and verification points
- Ensure drying validation addresses moisture traps and long CHT exposures

### How to get them cleaner, faster, and more consistently

- Start by validating decontamination cycles under challenging load conditions—low temperature pockets, high sorption materials, complex glove configurations
- Standardize glove port and interior cleaning motions to eliminate variability
- Map hinge lines, gaskets, and transfer ports as residue risk areas and incorporate them into the cycle design
- Use disinfectants compatible with high grade environments, ensuring residues from are fully removed first. Additionally, low-residue biocides can help reduce rinsing needs



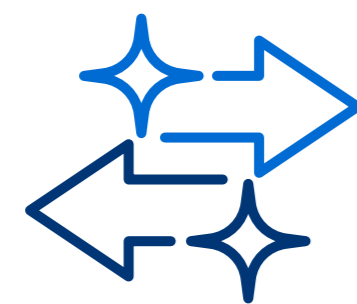
Where appropriate, integrated HPV bio-decontamination systems provide a consistent, operator independent method for achieving internal isolator control, complementing manual cleaning steps and improving repeatability.

# The Payoff - What All this Achieves

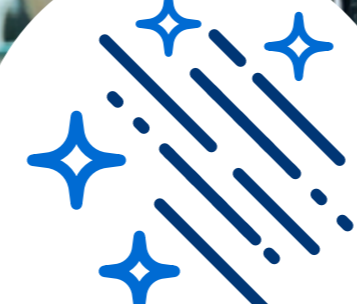
When cleaning optimization becomes a systematic,  
engineering driven practice:



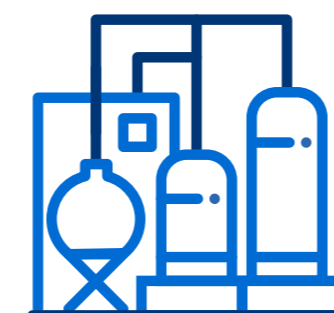
Changeovers shrink because cycle  
phases reflect actual residue behavior



Fewer deviations arise because worst case  
logic and hold time science are robust



Residue related re-cleans  
diminish



Consistent equipment readiness  
across isolators, bioreactors,  
and transfer lines  
*get "right first time cleaning" installed*



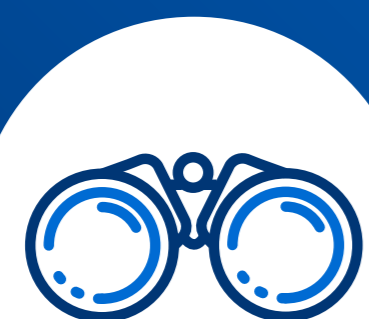
Faster validation execution because  
sampling, grouping, and documentation  
are structured



Cleaning stops being a constraint and  
becomes a controlled, repeatable process  
that protects capacity, supports scaleup,  
and accelerates time to market.

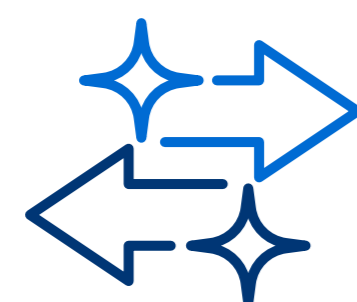
# How Partners can Help Accelerate this Work

Executing these improvements often calls for specialized expertise in cleaning science, contamination control, CIP/COP engineering, residue limit methodology, and digital validation design.



## Assess cleaning processes end to end

Reviewing cleanability and assess critical cleaning parameters using cleaning process development studies for different residues, considerations on equipment design, spray ball coverage, flow dynamics, CIP/COP sequencing, and operator driven variability.



## Support cleaning validation and re validation

From drafting protocols and sampling plans to developing hold time strategies, documenting worst case grouping, and preparing inspection ready evidence.



## Optimize cleaning programs scientifically

Using data on soil load, TTCF parameters, surface area analysis, and analytical method performance to reduce cycle time while maintaining validation grade control.



## Provide validated cleaning chemistries and disinfectants

That address proteinaceous soils, media residues, excipients, and low residue requirements for critical cleanrooms and isolators.



## Design and implement residue risk strategies

Including risk based sampling locations, recovery factor-aligned limit setting, and targeted controls for dead legs, shadow areas, and complex geometries.



## Introduce digital tools that streamline compliance

Such as electronic cleaning records, automated protocol/report generation, trend analysis dashboards, and integrated change control data flows for enhanced cleaning process understanding.

# How Partners Can Help Accelerate This Work

Ecolab brings all these capabilities together — validated chemistries, advanced CIP/COP engineering, global technical consultants, digital validation tools, and contamination control expertise — into a single, process driven approach.

This enables biopharma teams to engineer faster with more predictable cleaning cycles: shortening changeovers, reducing residue related failures, and progressing through validation cycles with greater confidence and speed.

The objective goes beyond cleaner equipment; it's about **maximizing equipment availability for manufacturing activities**, reducing deviations, and creating a smoother, more reliable path from development to commercial production.

To arrange an assessment  
of your facility, visit  
[ecolab.com/biopharmaprogram](https://ecolab.com/biopharmaprogram)

# With You Every Step of the Way



Drug Product Launch



Process Optimization



CAPA & Remediation

## Your Partner Across the Manufacturing Lifecycle

From new facility builds to process optimization and remediation, Ecolab Life Sciences delivers integrated contamination control solutions and expert guidance — helping you stay compliant, efficient, and ready for what's next.

To arrange an in-depth assessment of your facility, visit [ecolab.com/biopharmaprogram](https://ecolab.com/biopharmaprogram)

