WHITE PAPER

A Validation by Design Approach

Achieving Validated Cleaning in Pharmaceutical Manufacturing

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Abstract

Cleaning validation is a critical requirement in biopharmaceutical manufacturing. It helps ensure equipment is free from residues that could compromise product quality or patient safety, while preventing cross-contamination between batches. However, achieving and maintaining a validated cleaning process often becomes a significant operational bottleneck. This white paper explores the concept of Validation by Design, where the regulatory necessities for pharmaceutical manufacturing (such as cGMP, 21 CFR Part 211, EU GMP Annex 1 & 15, and ASME BPE) are engineered natively into washer/dryers. By integrating sanitary materials, optimized piping, automated process control, instrumentation monitoring, and GAMP 5-aligned software, pharmaceutical manufacturers can transition from reactive validation activities to a proactive, repeatable, and audit ready cleaning process for their component cleaning needs.

Glossary:

- **ALCOA+:** Principles (Attributable, Legible, Contemporaneous, Original, Accurate, Plus Complete, Consistent, Enduring, and Available) that form the foundation of Data Integrity.
- **ASME BPE:** American Society of Mechanical Engineers: Bioprocessing Equipment standards for the design and manufacturing of equipment used in biopharmaceutical production.
- **Dead Leg:** A pocket or area in a piping system where fluid can stagnate, typically measured as a ratio of length to diameter (e.g., ≤3D across the GEW cGMP Series).
- **GAMP 5:** Good Automated Manufacturing Practice, Version 5; a risk-based approach to compliant GxP computerized systems, established by the International Society for Pharmaceutical Engineering (ISPE).
- **Ra (Roughness Average):** A measure of surface texture; lower values indicate smoother surfaces (Ra between 0,5 and 0,6 µm is required for cGMP pharmaceutical manufacturing).
- **Sinner's Circle:** The four interdependent pillars of effective cleaning: Time, Temperature, Mechanical Action, and Chemical Action.
- **SPFR (Single Pass Final Rinse):** A process where fresh PW/WFI is used for the final rinse and then sent directly to drain to reduce the risk of cross-contamination.

The Foundation: Balancing the Sinner's Circle

The Theory of Efficacy

Effective cleaning in pharmaceutical manufacturing does not occur by chance. It results from the careful balancing of four interdependent variables collectively known as the Sinner's Circle: Temperature, Time, Mechanical Impingement, and Chemical Action. These variables operate as a dynamic equation—when one parameter is reduced, one or more of the others must be adjusted to maintain the required level of cleaning performance. For example, if temperature sensitive components cannot tolerate elevated wash temperatures, cleaning efficacy must be preserved through modifications such as extending cycle duration, increasing chemical concentration, or enhancing mechanical action.

While the Sinner's Circle provides the foundational framework for an effective cleaning process, additional procedural elements must also be defined, controlled, and incorporated into the cleaning SOP to ensure consistent and repeatable outcomes. These include: identification of components to be cleaned, including any required disassembly or breakdown steps; characterization of soils to be removed (e.g., product residues, API, excipients, microbial load); selection of the cleaning method, whether manual or automated; specification of cleaning agents, including type, concentration, and required volumes; definition of process parameters and acceptance criteria for cleaning verification; approval, release, and documentation steps for cleaned components.

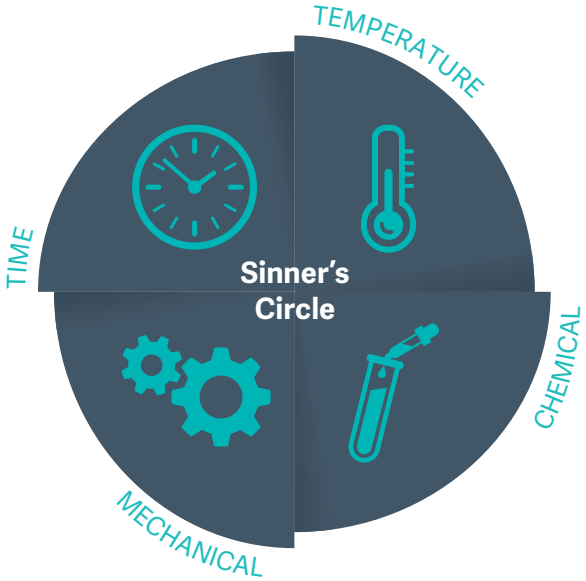
Only through precise and repeatable control of both the four variables of the Sinner's Circle and these procedural elements can cleaning processes be executed consistently, documented meaningfully, and confidently defended during regulatory inspection.

The Problem of Manual Variability

While manual cleaning may appear sufficient for limited, low-complexity cleaning tasks, it presents fundamental limitations when applied to the demands of pharmaceutical manufacturing. In manual component washing processes, certain factors in the Sinner's Circle are inherently difficult to regulate in a precise, repeatable way. Cycles often require additional time because mechanical impingement is limited to scrub brushes, sponges, and human force. Manual processes also cannot sustain the higher temperatures required by some applications, while automated systems can reliably deliver temperatures up to 93°C (199.4°F) over extended wash times.

The proper balance of detergents and additives is also more difficult to stabilize in the manual process and exposes the operator to harsh chemicals. Inconsistencies in manual detergent and additive dispensing can increase consumable costs and accelerate the buildup of chemical residues, eventually compromising component cleanliness. Measuring chemical, water, and energy usage in the manual washing process is nearly impossible from one operator or washing event to another, resulting in an unknown environmental impact and uncontrolled regulatory exposure.

Most critically, regardless of how precisely procedural guidelines are written, human error creates uncertainty in the quality outcome of a manual cleaning process. Because manual washing processes cannot be reliably standardized, the cleaning and drying of components can be compromised by residual process APIs (Active Pharmaceutical Ingredients) cleaning agents, or microbial soil, ultimately leading to potential batch cross-contamination or product quality failures.



While manual cleaning processes can be validated under certain limited circumstances, only automated washing solutions can reliably provide the efficiency, efficacy, repeatability, and consistency required to precisely balance the Sinner's Circle at the scale and complexity of modern pharmaceutical manufacturing.

Because repeatability in cleaning, elimination of cross-contamination, standardization of processes, and continuity of outcomes are critical to pharmaceutical manufacturing performance, the removal of human variability through automated component washing is a foundational investment in regulatory readiness.

Manual vs Automated Comparison

The following comparison illustrates the contrast between manual and automated approaches across the key dimensions of the Sinner's Circle.

Factor	Manual Method	Automatic Washer
Temperature	Restricted to safe and comfortable hand-washing temperatures	Higher temperatures not suitable for hand washing are precisely programmable
Time	Consumes labor; difficult to approximate or standardize	Precise timing once cycle starts; no labor involvement
Mechanical	Brush and sponge cleaning with variable force applied by different personnel	Exterior and interior cleaning through spray arms and injectors assure thorough cleaning and minimize breakage
Chemical	Manual measuring; concentrations uncertain	Automatic dosing of detergents and additives according to cycle programming
Detergent Consumption	Too much or too little depending on the operator	Precise, predictable, and cost-effective
Control Over Parameters	Analog; dependent on human performance	Digital; precise and documented
Cross-Contamination Risk	Difficult to prevent	The components are placed in their designated positions on the rack, as validated during the FAT, to ensure they are adequately covered by the water spray system (riboflavin test)
Process Documentation	Analog; depends on user adherence to protocol	Digital; cycle performance records maintained automatically (per audit trail CFR 21 part 11)
Repeatability of Results	Difficult to assure	Accurate and documentable

Regulatory Framework: Navigating Global Standards

Current Good Manufacturing Practices (cGMP)

The manufacture of pharmaceutical products is governed globally by a framework of current Good Manufacturing Practices (cGMP) that establish minimum requirements for facilities, equipment, and processes. Two regulatory systems form the primary reference standards worldwide.

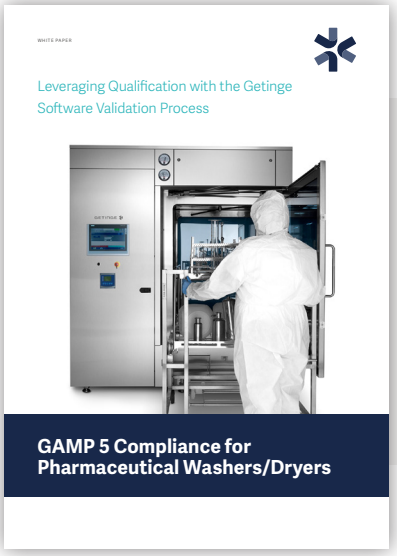
The EU GMP Guidance Annex 1 (Manufacturing of Sterile Medicinal Products) and the US FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing, Current Good Manufacturing Practice, define the classification and operational requirements for cleanrooms and clean zones where pharmaceutical components are processed. Both systems are used to regulate aseptic and terminal sterilization processes in the manufacture, control, and release of pharmaceutical products.

21 CFR Part 210 and 211 (US FDA)

Under the US Code of Federal Regulations, 21 CFR Part 211, current Good Manufacturing Practice for Finished Pharmaceuticals, Subpart D establishes specific requirements for equipment used in pharmaceutical manufacturing. Equipment must be constructed to facilitate cleaning, and cleaning procedures must be validated to prevent contamination and cross-contamination between product batches. Equipment cleaning and maintenance records must be maintained, and equipment must be cleaned and stored appropriately to prevent contamination that could alter the safety, identity, strength, quality, or purity of the drug product.

EU GMP Annex 15: Qualification and Validation

EU GMP Annex 15 establishes detailed expectations for cleaning validation within the European regulatory framework. Key requirements include the identification and justification of worst-case scenarios, the establishment of acceptance criteria for residue limits, and the execution of recovery studies to demonstrate that validated methods can detect residues at or below established thresholds. Annex 15 also mandates that cleaning validation cover the range of products and equipment configurations in use, with particular attention to shared equipment used across different product families. Ongoing verification following initial validation is expected to confirm that the validated state is maintained throughout the equipment lifecycle.



White Paper: GAMP 5 Compliance for Pharmaceutical Washers/Dryers

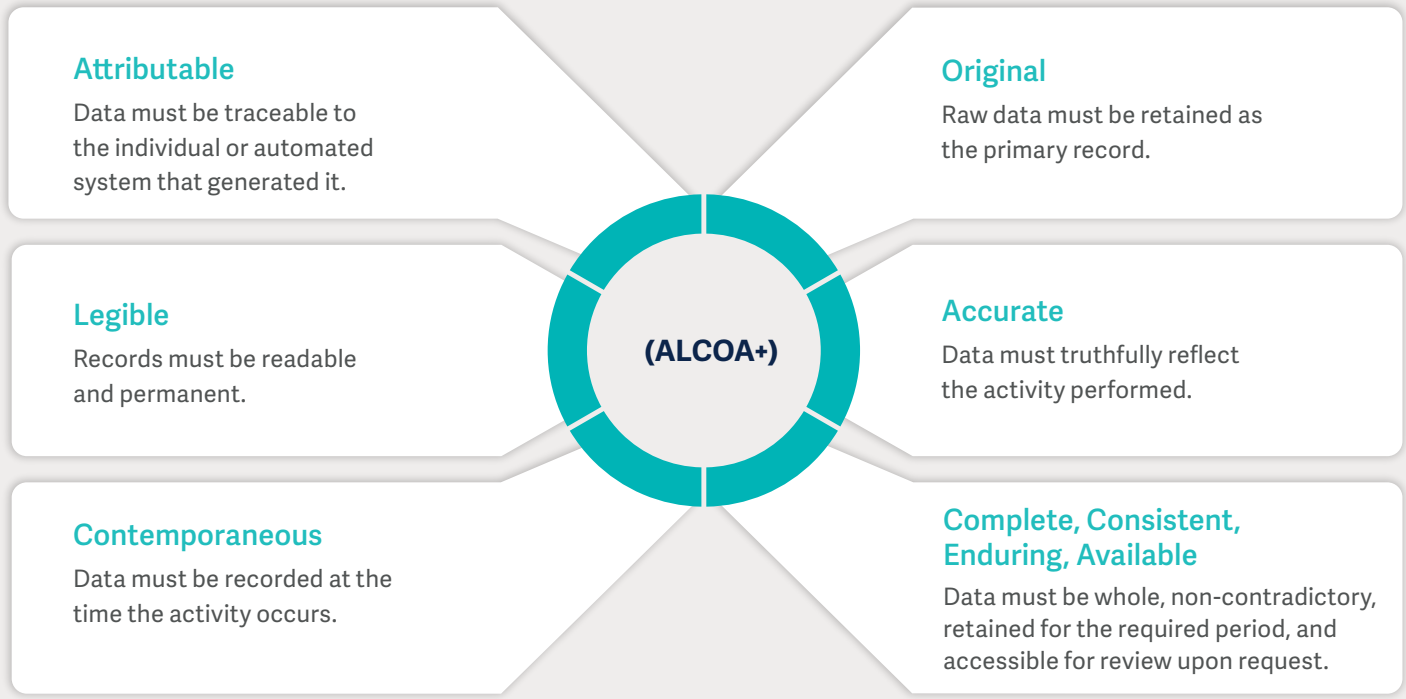
In the pharmaceutical industry, validation of automated equipment is essential, but can be costly and time-consuming. Regulatory frameworks like ISPE's GAMP 5 have raised expectations for data integrity and quality assurance in automated systems.

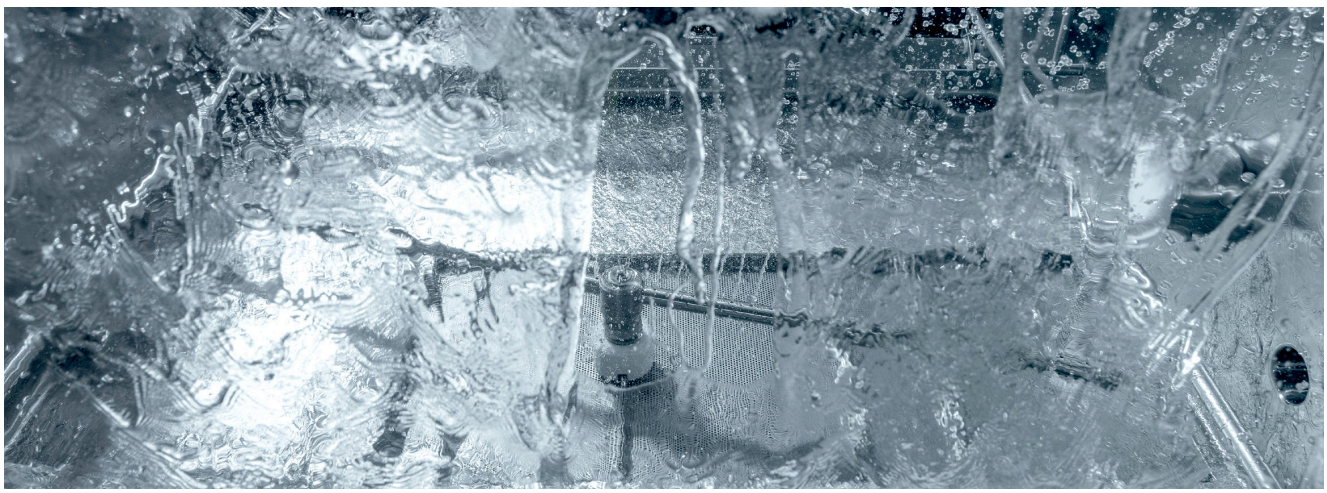
Learn more: getinge.com/dam/life-science/documents/english/gamp5-compliance-for-pharmaceutical-washers-dryers-113135-en.pdf

Data Integrity (ALCOA+)

Modern regulatory expectations for pharmaceutical manufacturing place significant emphasis on Data Integrity, the assurance that all data generated throughout the manufacturing process is complete, consistent, and accurate. Regulatory authorities worldwide align on the ALCOA+ principles as the foundational standard for compliant data.

For automated washing systems, this means that every cycle parameter including temperature, time, pressure, conductivity, and detergent dosing must be captured by the control system in a secure, tamper-evident electronic record that satisfies these principles and can withstand regulatory inspection.





Validation by Design: Engineering for Compliance

The concept of Validation by Design reflects a philosophy in which regulatory compliance is not an afterthought but is built into the equipment architecture from the earliest stages of design. For the Getinge GEW cGMP Series of washer/dryers, this approach manifests across materials selection, design, contamination control architecture, and rinsing methodology.

Sanitary Piping and Materials

All wetted metallic components within the Getinge GEW cGMP Series are manufactured from AISI 316L stainless steel, a material selected for its corrosion resistance, mechanical durability, and established history in pharmaceutical and bioprocessing applications. All non-metallic materials in contact with the process are FDA- or USP-approved. Internal system piping complies with ASME BPE standards and ISPE guidelines, ensuring that every surface along the water circulation pathway meets the quality standards expected in regulated biopharmaceutical environments.

Dead Leg Minimization

In pharmaceutical piping systems, a dead leg is a pocket or branch where fluid can stagnate and residue can accumulate, representing a significant validation risk. Stagnant water can harbor microbial contamination and prevent complete drainage and rinsing between cleaning phases, creating the potential for carryover between batches.

The Getinge GEW cGMP Series is designed with dead legs controlled to ≤3D across the product range, providing assurance of effective drainage and rinse water coverage.

The water pressure regulation system is optimized to ensure high-quality, efficient, and repeatable cleaning results throughout each cycle.

Contamination Control and Barrier Systems

Maintaining cleanroom classification integrity during component loading and unloading is a critical design requirement for pharmaceutical washers. The Getinge GEW cGMP Series incorporates door interlock systems to ensure that the clean and dirty sides of the washer cannot be simultaneously accessible, preventing the migration of contamination from the soiled loading area into the clean unloading area.

For configurations requiring an additional layer of contamination control, cross-contamination barriers (CCB) are available as an option on select models. This provides a configurable solution that allows facility managers to match the contamination barrier design to the specific cleanroom classification and risk profile of their operation.

Complete Range of cGMP GEW Washer/Dryers

GEW 888 neo
480 L (17 cu.ft.)

GEW 9109
810 L (29 cu.ft.)

GEW 101210
1212 L (43 cu.ft.)

GEW 131313
2146 L (76 cu.ft.)

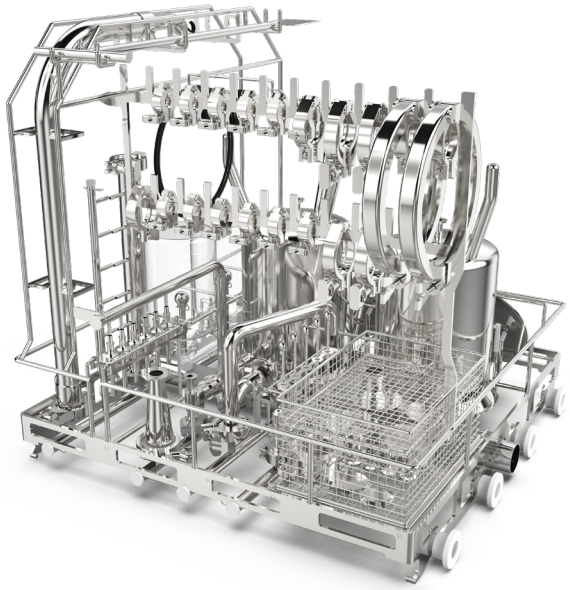
GEW 131820
4680 L (165 cu.ft.)

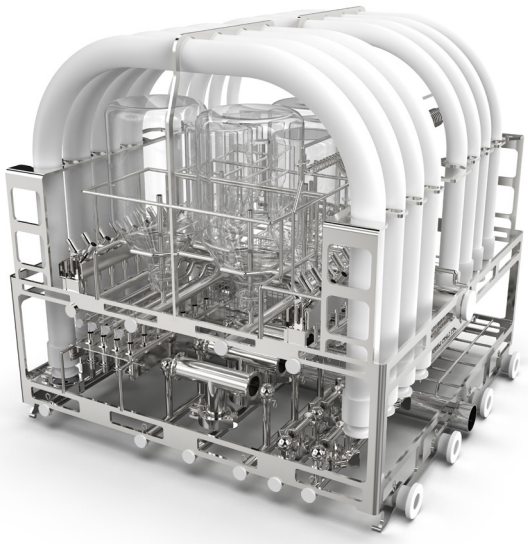
Custom Rack Design and Application-Specific Spray Configuration

No two pharmaceutical manufacturing operations are identical. Component cleaning validation is inherently load-specific, and the worst-case surfaces that must be reached, wetted, and rinsed are defined by the geometry and material composition of the specific components being cleaned.

To support validated cleaning across the widest possible range of pharmaceutical components, the Getinge GEW cGMP Series offers application-specific rack design and custom spray nozzle and spray ball configurations. Custom racks ensure that components are positioned to maximize spray impingement on critical surfaces, including interior channels, lumens, ports, and other difficult-to-access geometries. This capability is particularly relevant for cleaning validation studies that require documentation of worst-case scenarios, as it provides physical evidence that the most challenging surfaces can be reliably and repeatably wetted during the wash and rinse phases.

Typical applications include components from fill and finish operations, formulation equipment, silicone hoses, glassware, and filling line components, each of which presents unique load configuration and spray access requirements.





Final Rinse Solutions

The quality of the final rinse phase is among the most closely scrutinized aspects of a cleaning validation program. Industry practice and regulatory expectations generally recognize two approaches: recirculated rinsing, in which rinse water is cycled through the chamber repeatedly, and single-pass rinsing, in which fresh purified water or WFI passes over components once before being directed to drain. The appropriate method is selected based on site-specific validation requirements and the regulatory framework applicable to the facility.

GEW 888 neo

Getinge's GEW washer range accommodates both approaches across its product line. The GEW 131820 utilizes a standard recirculated rinse, providing thorough, validated rinsing performance suited to its high-volume washing demands. For mid-range models, the GEW 9109, GEW 101210, and GEW 131313, a Single Pass Final Rinse (SPFR) option is available, ensuring fresh purified water or WFI passes over components once and is directed immediately to drain, eliminating the risk of recontamination from recycled rinse water.

For the GEW 888 neo, Getinge has introduced a fully redesigned SPFR system that delivers single-pass rinsing quality in a significantly reduced footprint without increasing the washer's external dimensions. By replacing the large separate water tank required by conventional SPFR configurations with a compact hydraulic system and sanitary SPFR valves, water consumption is reduced to approximately 7 L (1.5 gal) per rinse cycle. Conductivity is monitored throughout the rinse phase; if levels exceed the validated range, a fault code is activated and the cycle is suspended, providing a critical in-process quality gate. The SPFR can be programmed as part of the validated cycle and configured to repeat as needed while maintaining the efficiency of the single-pass principle.

GEW 888 neo Single Pass Final Rinse Sequence

STEP 1 | PREPARATION
Rinse the hydraulic circuit as preparation for the single pass final rinse. Used water is immediately directed to the drain.

STEP 2
Prefill the loading rack and the lower spray wing within the chamber. Timer to be set for the duration of fill, which is dependent on the loading rack.

STEP 3
Fill the water tank in the hydraulic system. Meanwhile, the upper spray wing within the chamber will be activated for external rinse of components. Timer to be set for the duration of external rinse.

STEP 4
Push the collected water - through sterile compressed air - in the lower spray wing, loading rack and water tank through its nozzles and injector over the components to be rinsed.

STEP 5
A conductivity check is done on the final rinse to ensure no remaining soil.

Holistic, sustainable and cost-effective solution

Note: In case of a repeat final rinse, step 1 will only be done the first time and step 5 will only be done the last time. In between the sequence jumps from step 4 to step 2.

The Digital Validation Layer: Process Monitoring and Software Qualification

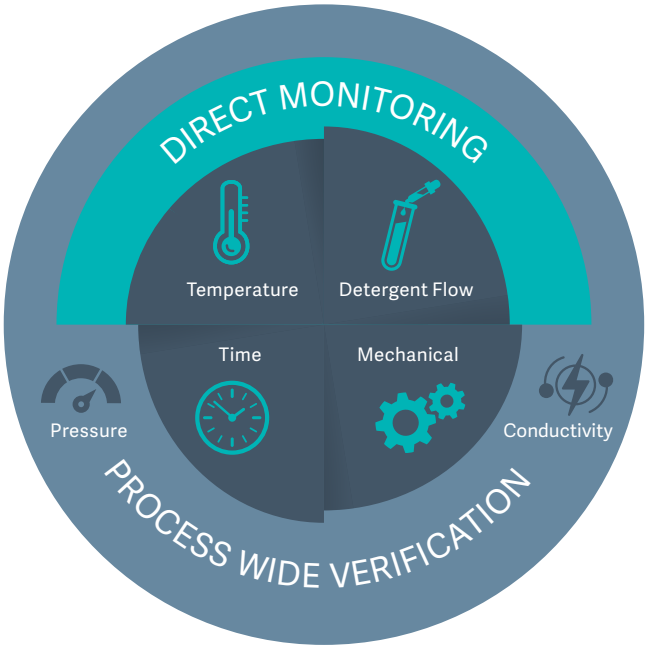
Real-Time Process Monitoring via Instrumentation

A validated cleaning process is not simply one that has been tested and documented once. It is a process that must be continuously confirmed to be operating within its validated parameters every time it runs. Real-time process monitoring through precision instrumentation is the mechanism by which this ongoing verification is achieved.

The Getinge GEW cGMP Series incorporates integrated sensors that provide continuous, real time monitoring of critical process parameters throughout every wash cycle. These sensors track key variables such as temperature, pressure, flow, and conductivity to ensure that each step of the cycle remains within the validated operating range.

While the process automation system ensures that the programmed cycle is executed according to the validated wash parameters, the sensors go a step further by confirming that the actual process conditions—those that directly impact cleaning performance—are consistently achieved. This dual layer approach of automation and sensor verification helps maintain process integrity cycle after cycle, reducing variability, enhancing compliance, and supporting a fully audit ready cleaning operation.

Software Process Monitoring



Key monitored parameters include:

Conductivity: Rinse water conductivity is monitored to verify that soil and process chemicals have been effectively removed. If conductivity drifts outside the validated range, the system generates an alarm and the cycle is suspended. This real-time conductivity data forms part of the cycle record and provides direct, quantitative evidence of rinse effectiveness for inclusion in the cleaning validation dossier.

Pressure: A dedicated pressure sensor continuously monitors pressure in the washer's hydraulic circuit throughout the wash cycle. The VSD + PLC program enables pressure PID regulation to maintain consistency and ensure adequate recycling pressure for fragile parts. This ensures that both the wash and rinse phases operate under the correct pressure conditions defined in the validated cycle parameters. Any deviation from the established pressure limits may indicate an improper load configuration or a mechanical fault. If such a deviation is detected, the system triggers an alarm and automatically suspends the cycle to prevent compromised cleaning results. The minimum and maximum pressure values observed during each phase of the cycle are recorded in the cycle record, providing direct, quantitative evidence of the mechanical action (pressure) achieved throughout the wash cycle.

Temperature: Continuous temperature monitoring confirms that the cycle is achieving and maintaining the required wash and rinse temperature at setpoint, the critical condition under which cleaning chemistry is active and effective. Temperature data provides the quantitative evidence needed to demonstrate that the thermal requirements of the validated process have been satisfied.

Detergent Flow: Monitoring of detergent and additive dosing confirms that chemical concentrations are being delivered consistently and accurately for each cycle, supporting the chemical action element of the Sinner's Circle.

Together, these monitoring capabilities provide the continuous process verification data required by modern regulatory expectations, creating a digital record of every cycle that can be reviewed, trended, and audited to confirm the ongoing validity of the cleaning process.

*Options can be added that could change the number of sensors.

Risk-Based Software Validation: The Getinge Software Validation Process

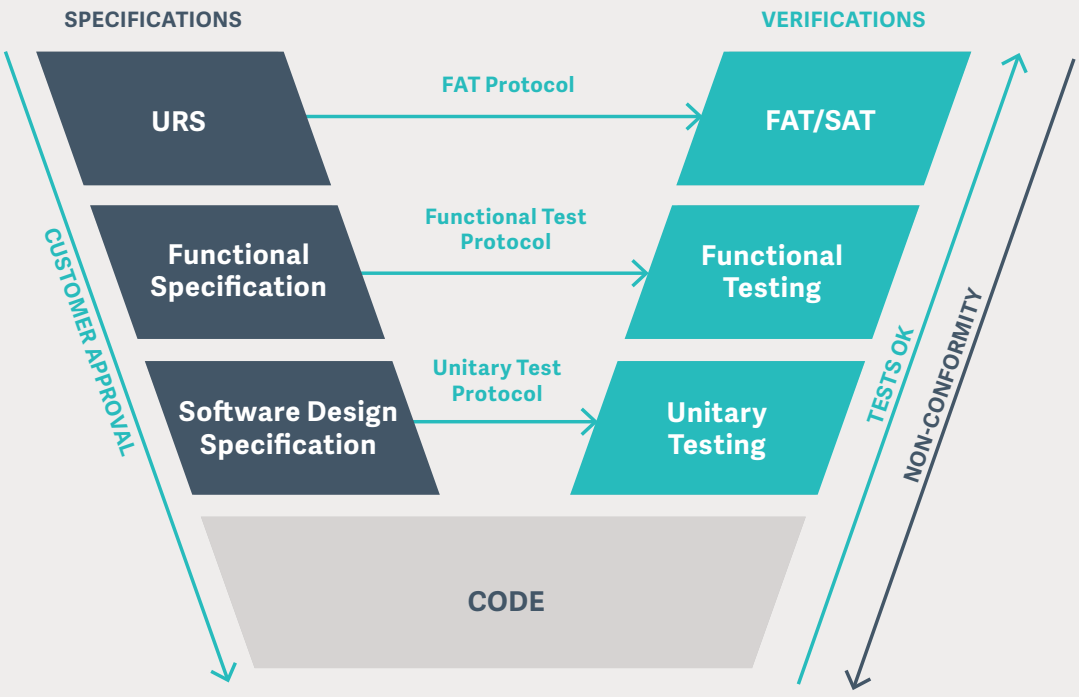
For pharmaceutical manufacturers, the software controlling a cGMP washer/dryer is not simply an operational convenience. It is a regulated system that must itself be validated. The GAMP 5 framework, established by the International Society for Pharmaceutical Engineering (ISPE), governs this requirement through a risk-based lifecycle approach that mandates validation effort proportional to the risk the system poses to product quality and patient safety.

Getinge addresses this industry challenge by providing a rigorously pre-validated software foundation known as the Getinge Software Validation Process. This is a master software baseline for all cGMP washers/dryers, developed and maintained under a formal V-Model lifecycle, ensuring that the vast majority of core automation functionality is already verified and documented before the equipment reaches the customer's site.

The formal documentation suite supporting the Getinge Software Validation Process includes the Functional Design Specification (FDS), Hardware Design Specification (HDS), and Software Design Specification (SDS), all of which are traceable to the User Requirement Specification (URS). A formal, documented software risk assessment is performed for the entire process, determining the residual validation effort required at the customer's site and ensuring that site-based testing (FAT/SAT) is focused on high-impact or configurable elements only.

A key differentiator of the Getinge approach is the strategic application of GAMP 5 software categorization, which directly reduces the validation burden borne by the customer's team at site acceptance. The Getinge Software Validation Process maximizes the use of GAMP 5 Category 4 (Configured Product) elements, which are standard, configurable software components such as PLC logic and SCADA customized within defined limits. Because the core functionality is Category 4 and fully validated by Getinge at the factory, customers need only verify their site-specific configurations, rather than re-testing the underlying base code. Category 5 (Customized Software) elements, meaning bespoke code or non-standard configurations, are reserved only for unique customer-specific functions, minimizing testing risk and reducing overall validation time.

All artifacts supporting the process validation, configuration records, and delivery risk assessments are provided to the customer as part of the full validation package, streamlining customer audits and regulatory inspections. All Getinge team members working on customer projects are trained and certified according to the automation documentation present in the Quality Management System (QMS), consistent with GAMP 5 training requirements.



Implementation Profile: The GEW cGMP Series

Versatility in Application

The Validation by Design principles described throughout this paper are implemented across the full Getinge GEW cGMP Series, a scalable range of washer/dryers designed to accommodate the full spectrum of pharmaceutical manufacturing environments and throughput requirements.

The GEW 888 neo represents the compact implementation, designed specifically for small cleanrooms and clean spaces where floor space is at a premium. With a chamber volume of 480 L (17 cu.ft.) and a total footprint of 1.3 square meters (14 ft^2), the GEW 888 neo delivers high-throughput, validated component cleaning in environments where larger equipment is not feasible. For operations requiring greater capacity, the GEW Series scales through the GEW 9109 (810 L / 29 cu.ft.), GEW 101210 (1,212 L / 43 cu.ft.), GEW 131313 (2,146 L / 76 cu.ft.), and the large-format GEW 131820 (4,680 L / 165 cu.ft.), with each model incorporating the same core Validation by Design engineering principles.

All models in the series support pharmaceutical manufacturing applications spanning a wide range of component types, including:

- **Fill and finish components:** Filling needles, pistons, and product contact parts from aseptic filling lines
- **Formulation equipment:** Vessels, agitator blades, and transfer components from liquid formulation operations
- **Flexible components:** Silicone hoses, tubing, gaskets, and flexible connections used throughout manufacturing
- **Glassware:** Beakers, flasks, cylinders, and analytical vessels from quality control laboratories

This breadth of application coverage reflects the universal relevance of validated automated washing across the pharmaceutical manufacturing enterprise, from early-stage QC laboratory operations through large-scale commercial production.

Operational Validation (OQ)

Operational Qualification confirms that the washer/dryer operates consistently within its specified parameters across the full range of conditions defined in the validated process. The digital process monitoring capabilities of the GEW cGMP Series, including continuous temperature, pressure, conductivity, and detergent flow monitoring, provide the repeatable, quantitative cycle data required to successfully execute and document OQ protocols.

For each validated cycle, the control system generates a complete cycle record that captures all critical parameters throughout the wash, rinse, and drying phases. These records satisfy FDA 21 CFR Part 11 requirements for electronic records and signatures and provide the documented evidence base that regulatory inspectors require to confirm the validated state of the cleaning process.

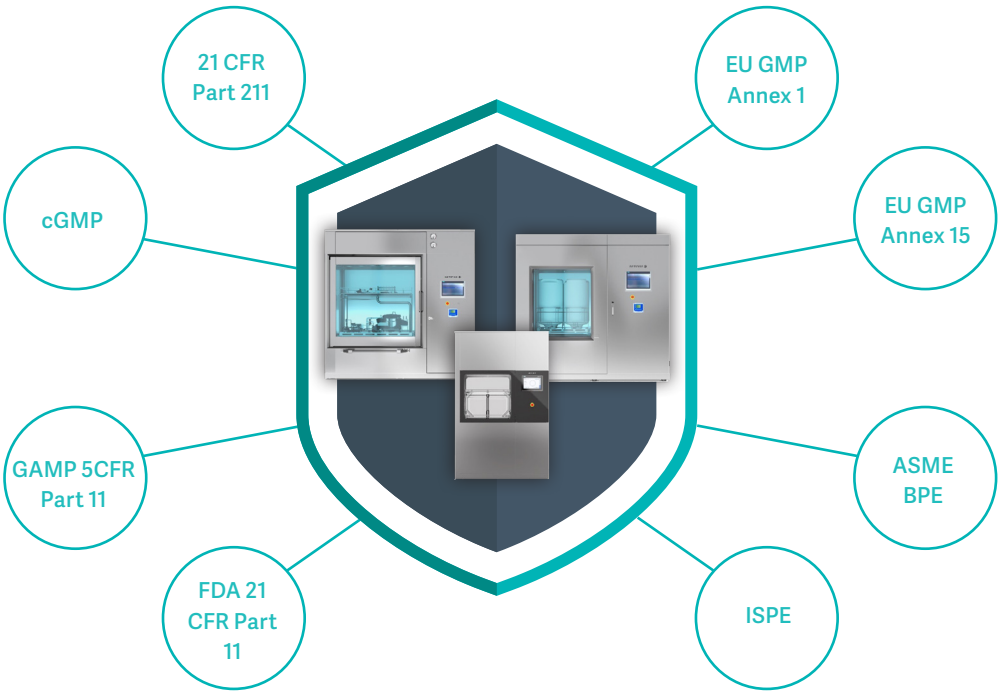
Where the final rinse or recirculated final rinse method involves a single-pass approach, conductivity monitoring of the final rinse phase provides a real-time, quantitative pass/fail gate that is automatically recorded as part of the cycle documentation, simplifying the correlation between OQ test results and ongoing production cycle records.

Conclusion

Cleaning validation in pharmaceutical manufacturing is ultimately a statement of confidence: confidence that every cleaning cycle delivers the same result, that every result is documented, and that every document reflects what actually occurred. Achieving and sustaining that confidence requires equipment designed from the ground up to support it.

Getinge is not simply a supplier of washer/dryer equipment. Getinge is a partner in regulatory compliance, one that has engineered the requirements of cGMP, 21 CFR Part 211, EU GMP Annex 1 and Annex 15, ASME BPE, ISPE, FDA 21 CFR Part 11, and GAMP 5 directly into the architecture of every GEW cGMP Series washer/dryer. From the AISI 316L stainless steel piping that meets ASME BPE standards, to the door interlocks that protect cleanroom classification, to the pre-validated software baseline that reduces site qualification burden, every design decision reflects a commitment to making validation not harder but engineered in from the start.

For pharmaceutical manufacturers facing the combined pressures of regulatory scrutiny, operational throughput demands, and the imperative to reduce time-to-market, the choice of cleaning equipment is a strategic decision. Choosing Getinge means choosing a validated state that is designed to be achieved, documented, and maintained from commissioning through the full productive life of the equipment.



Pharmaceutical Production Solutions

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