



# Bioreactor preparation solutions

Specialty wash rack assures validated cleaning in advance of sterilization.

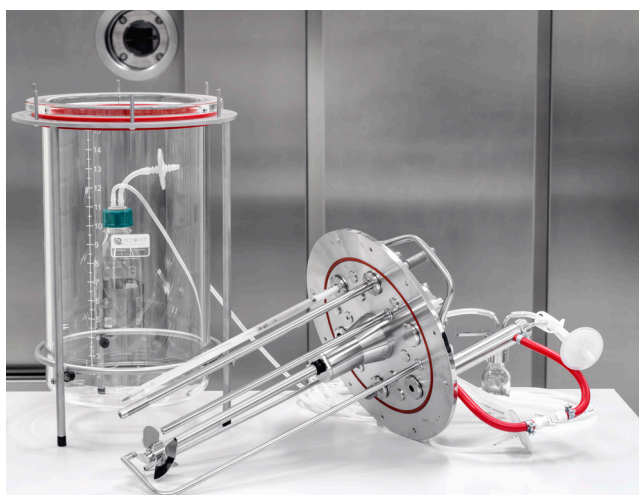
# Advances in bioreactor washing

The programmable labware washer with specialty bioreactor wash rack assures thorough cleaning, better reproducibility, and reduced labor.

## Abstract

Proper preparation of a multi-use bioreactor is suggested in order to increase productivity, reproducibility, and to avoid process interruptions that are required for a thorough cleaning of the vessel and all associated components. Bioreactors commonly used in pharmaceutical, biotechnology, vaccine, and biological research require cleaning and subsequent sterilization between same-work sequences or before new applications are initiated. Protocols for these cleaning and sterilization scenarios are typically established by internal or third-party compliance and oversight agencies. Once adopted, however, these protocols must be implemented within a standard

operating procedure that is central to the facility operation. Any design or process advantages that can contribute to efficient cleaning prior to sterilization, including the bioreactor assembly and the labware washer, can offer internally measured life cycle savings in labor, improved throughput, and predictable use of detergents and additives. This paper illustrates the symbiotic relationship between bioreactor design and glassware washer engineering that is specially configured to minimize work, assure predictable outcomes, and take advantage of the benefits of pre-validation enabled by the bioreactor and lab washer loading wash racks when used in sequence.



The Applikon multi-use bioreactor can be partially or fully disassembled prior to washing, depending on next process criteria.



Process	Components	Gaskets and Seals	Silicon Tubing
<b>Repeat</b>	Most components remain in place. Sensors are removed and cleaned manually as usual.	O-rings can remain in place	Tubing can remain in place to connect to washer rack injector inlets
<b>New</b>	All components are easily removed. Sensors are cleaned manually as usual.	All O-ring must be replaced	Existing tubing must be removed and replaced

## Getinge and Applikon: A Holistic Solution

Getinge is a leading global provider of products and solutions that contribute to quality enhancement and cost efficiency within healthcare and life sciences. Through the efforts of more than 10,000 people in 38 countries, Getinge has established a presence in life science, pharmaceutical, and biotechnology research based on a product line continuum where one product line or service complements another. The company's proficiency in design, production, and validated installation of sterilizers for laboratory, hospital, and pharmaceutical production facilities has evolved over generations of advances in science and medicine. In 1994, Getinge acquired the assets of a leading manufacturer of high-performance labware washing systems widely used around the world. This established a practical solution for sequential cleaning and sterilization of equipment and instrumentation.

Most recently, with the acquisition of Applikon Biotechnology in 2020, Getinge's product development teams have committed resources to explore engineering solutions to create a seamless, pre-validated combination of multi-use bioreactor design and unique labware washer loading rack configuration to prepare the bioreactor for sterilization. The Applikon brand is a world leader in development of advanced bioreactor systems for production of vaccines, antibodies, tissues, biopharmaceuticals, nutraceuticals, and biosimilars in the pharmaceutical industry as well as enzymes, food, feed, bio-fuel, bio-chemicals, and bio-plastics for industrial biotechnology.

Today, Getinge has created a unique solution to bioreactor preparation in support of pharmaceutical manufacturing and associated applications through a broad range of research and production disciplines. This multidisciplinary expertise has established a synergistic process proven to predict and more efficiently use detergents and additives.

### Overcoming the Challenges and Benefits of Overlapping Technologies

Among the most important outcomes of this combination is the opportunity to return a clean bioreactor to production as a pre-validated component in a highly regulated industry. The design of a flexible labware washing loading rack assures a repeatable protocol for comprehensive cleaning bioburden, from the bioreactor and head plate, to optimize sterilization. Depending on how the bioreactor is used, whether for repeated processes or starting new processes, selected components on the head plate can remain installed for cleaning and removal of bioburden. Either way, use of the configurable loading rack helps increase turn-around time, reduce labor, and assure compliance from start to finish.

### Who Benefits?

The Applikon multi-use bioreactor is used in academic, government, and biopharmaceutical laboratories for benchtop research. Typical applications include cell culture growth, cell production, and microbiological fermentation. Those responsible for acquisition and operation include the end users themselves as well as facility and maintenance managers, lab managers, and quality assurance supervisors charged with compliance and product viability.

Specific benefits of the bioreactor design concurrent with the design of removable wash racks include personnel safety, ergonomics, preparation for transition from BSL3 to BSL1 or BSL2 areas, and fewer chances of reactor vessel breakage or component damage.

By establishing routine processes for dismantling and cleaning, the laboratory can enhance reproducibility from one procedure to the next while accelerating throughput and minimizing downtime.

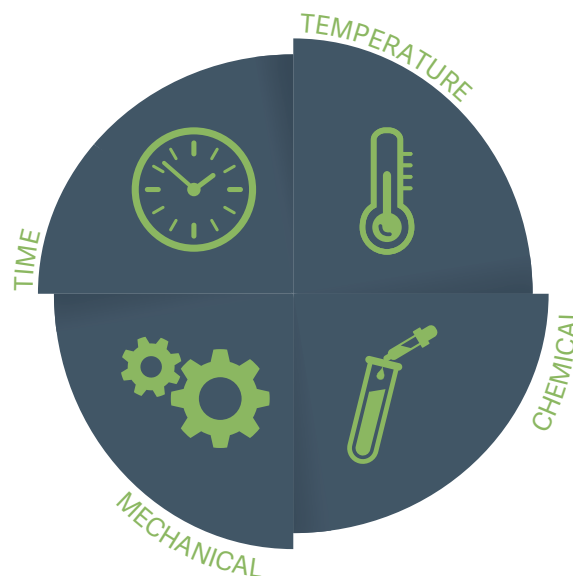
In particular, the ability to clean and sterilize the bioreactor within a pre-validated process assures repeatability when used from lab to lab and among multiple personnel of various skill levels.

# Automated Washing Assures Reproducibility

In addition to the specially designed wash rack, a key factor in repeatability in multi-use bioreactor washing is the programmable washer controller.<sup>1</sup> This controller permits the user to initiate completely automated washing functions that offer significant benefits over manual washing.<sup>2</sup> The newly formed, multi-disciplinary team established during the acquisition of Applikon has merged tested processes that can be approved and integrated into the laboratory standard operating procedures. These procedures assure accurate cycle replication without deviation from performance that is essential to pre-validation. Getinge technical support can also assist in developing new or amending current procedures to comply with your specific process needs.

## Benefits of Automated Washing

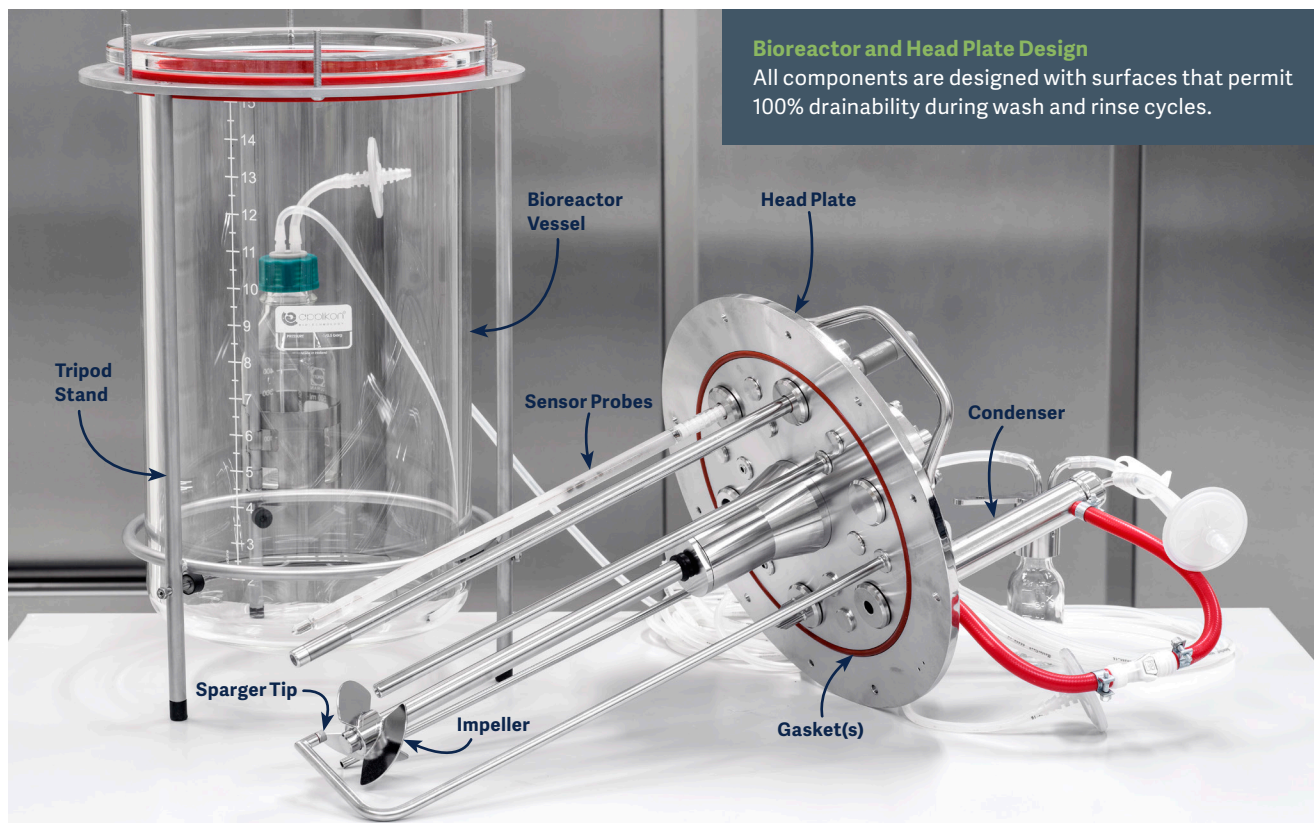
- Cycle phases can be programmed with time, temperature, chemical and mechanical impingement as adopted in the standard operating procedure
- Chemical handling is minimized; volume of chemicals and additives is specific to the process and predicted
- Bioreactor handling is reduced and ergonomics are improved over manual cleaning
- Water consumption can be predicted, controlled and ultimately reduced
- Overall labor and operator error is reduced



## Wash Cycles

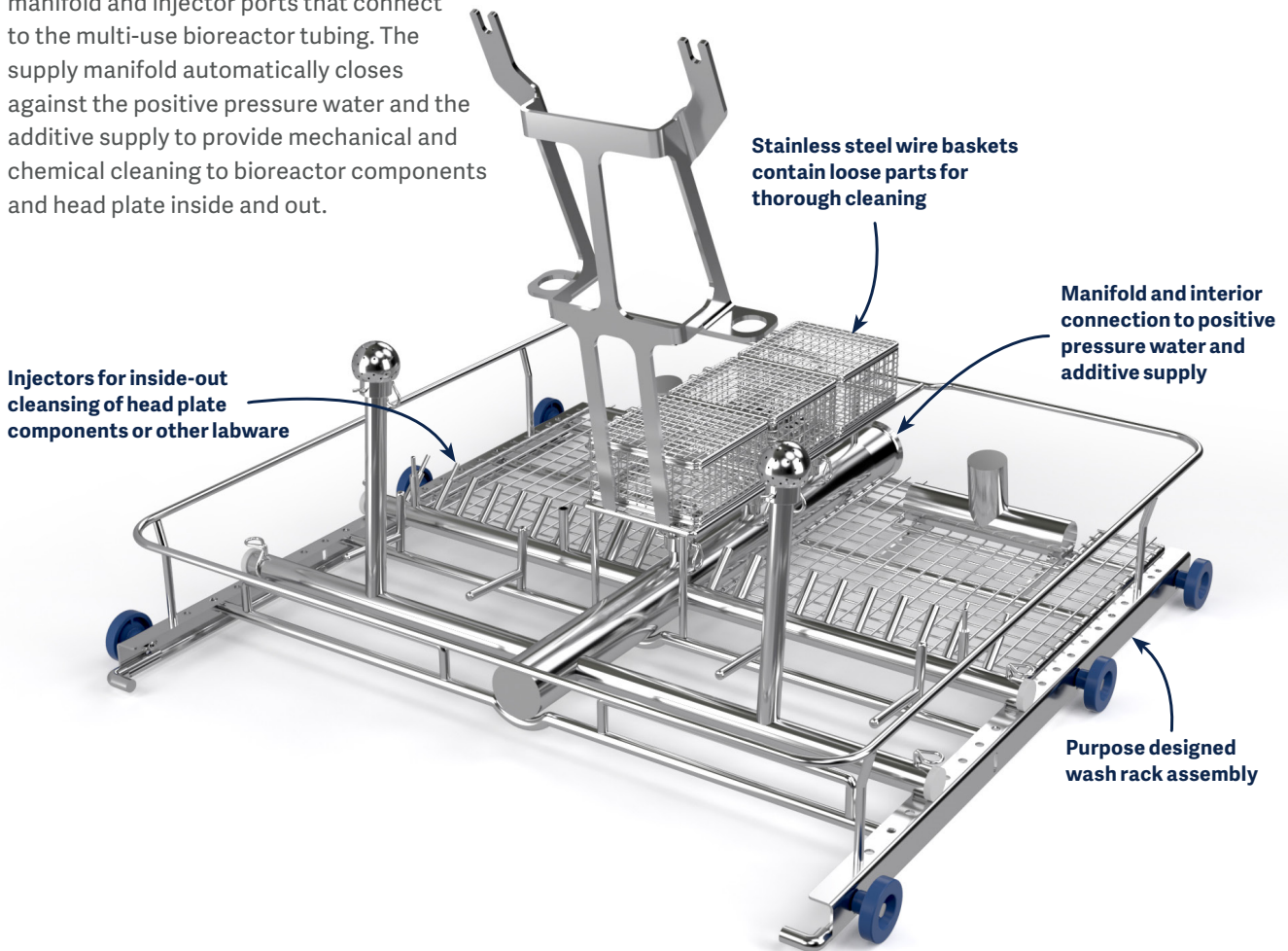
Typical programmable cycles are flexible to accommodate different soils and the variety of chemicals, detergents and additives required. Pre-treatment typically includes a manual cold soak with NaOH.

- Pre-treatment prewash as required
- Wash
- Running water rinses
- Demineralized water rinses
- Final demineralized water rinse
- Drying
- Cooling



## Labware Washer Loading Rack Design

This illustration of the removable wash rack indicates the key features of the manifold and injector ports that connect to the multi-use bioreactor tubing. The supply manifold automatically closes against the positive pressure water and the additive supply to provide mechanical and chemical cleaning to bioreactor components and head plate inside and out.



## Loading Steps

Step	Description
<b>1. Dismantle the bioreactor</b>	
a. Prepare the head plate for repeat process	Remove probes for manual wash; other components remain intact
b. Dismantle the head plate for new process	Remove all
<b>2. Load wash rack</b>	
a. Vessel and tripod	Position for proper drainage
b. Load head plate	Position for proper drainage
c. Head plate tubes	Connect to injectors via flexible tubing for maximum interior clean-out
d. Miscellaneous parts	Load into mesh basket as required Impeller locking Allen screws should be replaced if worn
e. Close condenser openings	Cover with foil or silicone cap
f. Remove O rings and gaskets	Only required if New Process is next; if Repeat Process is next, this step is not required due to head plate design

## Getting Lancer Ultima laboratory washers

The Getinge Lancer Ultima series washers include nine high-performance models that offer a range of labware loading options depending on the research taking place.



Basic range	Models	Control system	Advanced range	Models	Control system
<b>Undercounter</b>	810LX 815LX 820LX	Prolux 3.5" HMI	<b>Freestanding</b>	1400LXP 1600LXP 1600LXP-H250 1800LXA	Prolux Plus 7" HMI
<b>Freestanding</b>	910LX 1300LX 1400LX	Prolux 3.5" HMI			

## Next Steps: Sterilization

Proper washing of the bioreactor, head plate and associated components is a critical prerequisite to successful sterilization. The bioreactor and head plate design, coupled with the removable wash rack with multiple injector tubes, completes the necessary first steps in preparation for a bioreactor turn-around within the parameters of a pre-validation program. Best practices for sterilization are outlined in a Getinge Application Brief.<sup>3</sup> Here, the benefits of pre-programmed sterilization functions such as, vacuum and pressure sequences, ramp, dwell, cool-down, air-over-pressure and drain cycles provide a complementary transition as the bioreactor is returned to service.



Bioreactor headplate components can be prepared differently for new or repeat applications.

Bioreactor Preparation	For New Process	For Repeat Process	Note
Review approved protocol for loading and washing	Yes	If Mandated	Established by management
Remove sensors	Yes	Yes	Sensors are not to be cleaned in the washer; refer to manufacturers' instructions in sensor cleaning
Remove, inspect and/or replace filters	Yes	Yes	Remove prior to washing and inspect
Remove tubing from addition ports	Yes	No	Only when damaged
Remove head plate	Yes	Yes	No tools required
Separate glass vessel from tripod stand	Yes	No	No tools required
Remove air inlet pipe	Yes	Yes	Porous sparger is cleaned separately according to manufacturers' recommendations
Remove impeller from stirrer	Yes	No	Allen key required
Remove stirrer from head plate	Yes	No	Tools are required for 15L and 20L vessels and for magnetically coupled stirrers in 2 – 7 L vessels
Remove head plate O-ring	Yes	No	Common tools may be required
Remove inserts from head plate	Yes	No	Tools required only when sticky
Remove the off-gas outlet pipe and condenser	Yes	No	Disassemble for new process; determine in advance whether this must be washed separately
Cap condenser tubing connections on condenser jacket	Not Applicable	Yes	Cover with foil or silicone cap
Remove septa or blocked ports	Yes	No	As required
Arrange bioreactor components in washer loading rack	Yes	Yes	Check to make sure all components are oriented to aid in draining
Connect injectors to separate components for inside-out cleaning	Yes	Yes	Injectors not in use may remain open or may be capped based on validation directives
Use washer basket for miscellaneous parts	Yes	Yes	If required

## Conclusion

The combination of the Applikon multi-use bioreactor, together with the programmable labware washer and specialty bioreactor wash rack, establishes a highly reproducible system with significant benefits that reduce labor, increase throughput, minimize downtime and yield

a clean bioreactor ready for final sterilization. The combination of pre-validated washing and sterilization performed in the washer and sterilizer maintain an approved standard for quality control that reduces the chance of human error or deviation from proven process.



Getinge Lancer Ultima laboratory washer, model 910LX loaded with 3L bioreactor in wash rack.



Once the bioreactor and associated components are cleaned, a programmable sterilization cycle assures final preparation in compliance with protocols essential for validation.



## References

1. For a detailed description of the Getinge Lancer Ultima Series labware washer refer to our website:  
<https://www.getinge.com/us/product-catalog/lancer-ultima-series-freestanding-laboratory-washers/>  
<https://www.getinge.com/us/product-catalog/lancer-ultima-series-undercounter-laboratory-washers/>
2. For a complete description of the benefits between automated vs. manual washing refer to our website:  
<https://www.getinge.com/us/clinical-insights/research-laboratories/the-4-pillars-of-successful-labware-cleaning/>
3. See Getinge Application Brief: Best Practices for Multi-use Bioreactor Sterilization



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