Drug product filtration system

STERILE FILTRATION

The drug product filtration system has been designed to support EU GMP Annex 1: Manufacture of sterile medicinal products requirements for contamination control strategies with automated *in situ* pre-use post-sterilization integrity testing (PUPSIT) and post-use integrity testing of sterile filters, as well as, a pre-use flow kit leak test (Fig 1). The system utilizes single-use technology (SUT) to ensure faster turnaround between product batches, eliminating the need for clean-in-place (CIP) and sterilization-in-place (SIP) operations and associated cleaning validation, reducing maintenance costs and system downtime, thereby ensuring increased plant productivity. It operates using configurable recipe-controlled phases to automatically perform terminal sterilization prior to filling with maximum product recovery using standard flow kits. It supports both constant and intermittent filling so that all common approaches to filling can be accommodated.

Key features and benefits

- Fully automated sterile filtration with configurable recipe-controlled phases
- Automated PUPSIT and post-use integrity testing
- Enhanced product recovery method for reduced product loss
- Single-use flow kits for rapid turnaround between batches
- One system for both single and redundant filtration configurations
- Comprehensive filter area coverage for wide range of batch volumes

Automated leak and integrity testing

A Palltronic Flowstar LGR integrity test instrument has been integrated to perform PUPSIT and post-use integrity testing of liquid filter capsules. Leak testing of the single-use flow paths can also be carried out, ensuring the main flow kit is defect-free before committing product to the system. The flow kits include a sterile gas vent filter to support the priming and venting for the integrity testing procedures. Testing is incorporated into the batch recipe for the process for full automation. The system can perform both bubble point and forward flow integrity testing methods to support all industry acceptable testing methods for liquid filters.

Fig 1. The drug product filtration system performs automated *in situ* pre-use post-sterilization integrity testing (PUPSIT) and post-use integrity testing of sterile filters, as well as, a pre-use flow kit leak test in support of contamination control strategies.

Minimized product loss

Typical filtration product recovery, using a combination of pump draining and air blown down, allows a certain volume of process fluid to be recovered. Our drug product filtration system has a patented method for enhanced product recovery to ensure minimal product loss within the entire system flow path. This includes the addition of a pump to recover product from the filter core which increases the product recovery by up to 54% compared to pump draining and air blown down procedures alone (Fig 2).

Fig 2. Recovery pump and bag for enhanced product recovery located on the drug product filtration system.

Comprehensive filter area coverage

The drug product filtration system design enables process flexibility because of its compatibility with a large range of filter sizes, from small KA1 filter capsules up to 10-inch filter capsules. This enables compatibility with a wide variety of different drug product formulations and batch volume sizes all on the same system. The system is also filter agnostic enabling other vendor filter capsules to be incorporated as required into the flow kit.

Filtration redundancy

The system can support flow kits including a single sterilizing grade filter capsule configuration or a redundant filter configuration (Fig 3). Filter redundancy can reduce the risk of repeating batch processing due to a failure of post-use integrity testing of the primary sterilizing grade filter. The system can automatically conduct PUPSIT and post-use integrity testing on both primary and redundant filters.

Our irradiated antifoam products are provided in single-use bags with convenient tubing and fitting designs (Fig 2 to 4). The single-use bags can also be customized to fit your specific needs.

Flow kits

The single-use flow kit has been designed for easy installation and removal, with a shadow board on the system surface to visibly guide the user reducing the risk of human error. Standard flow kits are available for the system incorporating our 0.2 µm sterilizing grade filters. Each flow kit comes double bagged, gamma irradiated with a sterile claim. Standard flow fits use Kleenpak™ Presto sterile connectors and disconnectors for installation and uninstallation of the flow kit. Custom flow kits incorporating other commercially available sterilizing grade filters and sterile connectors are available on request.

(A)

(B)

Fig 3. Two flow kit types are available for the drug product filtration system either single or redundant. (A) single sterilizing grade filter configuration; (B) redundant filter configuration where a second sterilizing grade filter is present in series.

HMI and system control

The drug product filtration system has an adjustable integrated touchscreen human machine interface (HMI), which shows the process instrumentation diagram (PID) and batch processing overview screens with real-time process pictures showing the current flow path, valve positions, and monitored values (Fig 4).

The software provides intuitive and flexible method creation, automated system control, and process evaluation to simplify your filtration tasks, ensuring consistent processing. With the help of a wide variety of control features, the user can tailor the system's filtration controls to most processing requirements.

Visual instructions for installation (IFI) are accessible via the HMI screen providing operators with a step-by-step guide to installing the single-use flow paths and making the relevant fluid connections.

The software is designed according to GAMP 5 guidelines (ISPE) and enables work in compliance with US FDA 21 CFR Part 11 regulation. The software supports full data integrity and consistency throughout the process, enabling digitized and validated manufacturing set-up. Process data is reliably stored in a database repository. For access control, the software is secured by a password-protected user login. User activities are logged in the system logs for usage history. The software provides the ability to generate reports, and data can be exported in a tabular spreadsheet.

Process monitoring and control

The fully automated and recipe driven batch processing enables a wide range of process control methods to control functions such as flow control and differential pressure that covers the majority of sterile filtration process strategies. Optional process temperature monitoring is available if required.

Automation

Configurable recipe-controlled phases to automatically perform each phase of the filling process including:

- Flow kit leak testing
- Flow kit and filter priming
- PUPSIT
- Product filtration
- Product recovery
- Post-use integrity testing

Batch records

Upon operator selection, batch reports will be generated automatically at the end of a batch for each step. Sample batch reports can be provided upon request. Predefined batch records contain the following information:

- General batch information, phase information, and transition conditions
- Single-use flow kits and filters used for the batch
- Global and recipe parameters
- Audit trail excerpts
- Alarms summary

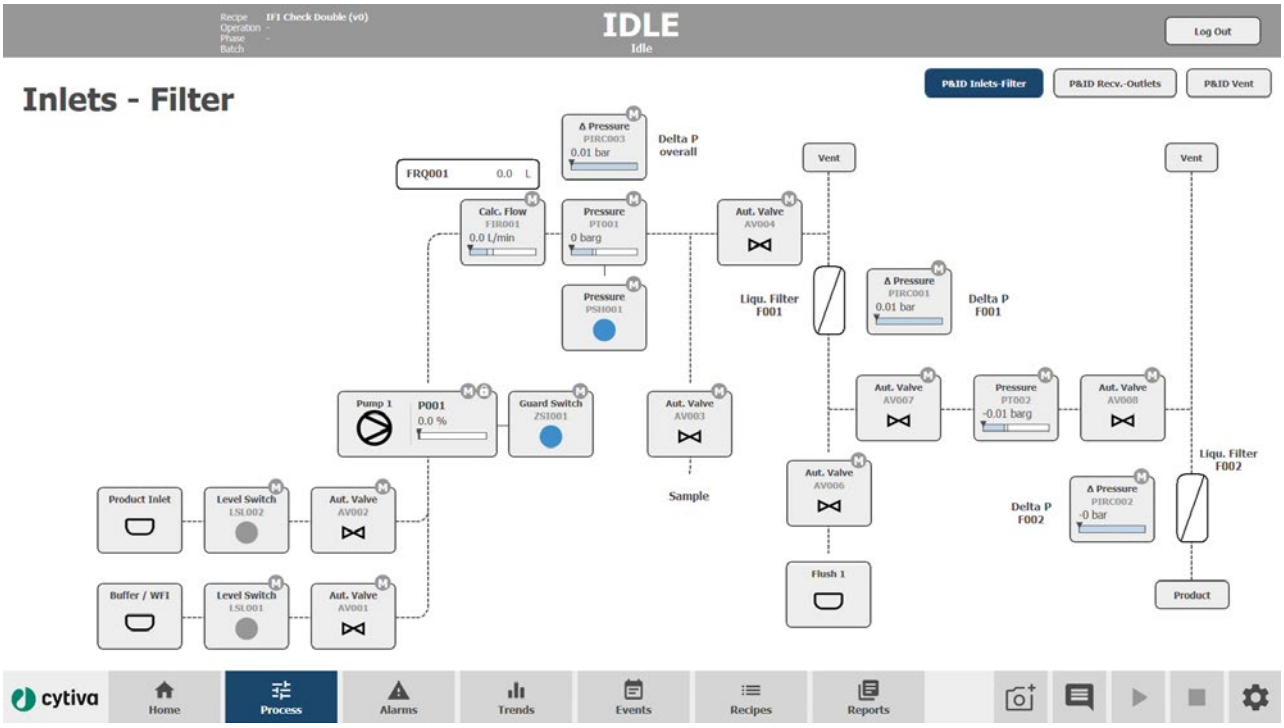

Fig 4. The drug product filtration system HMI showing the PID screen.

Connectivity

The system can be connected to our LevMixer™ system as a feed tank or intermediate tank. Additionally, our single-use transfer sets and filling flow kits with Allegro™ filling needles are available to complete your filling solution.

To enable communication between the system and other equipment in the filling line, the system uses OPC UA client as standard. This enables control signals to be given and received from the filling line, including process pauses, as required.

Regulatory

The drug product filtration system provides a detailed validation package for all configurations according to ASTM 2500 standards (a standard guide for specification, design, and verification of pharmaceutical and biopharmaceutical manufacturing systems and equipment). The regulatory dossier includes:

- Regulatory compliance ROHS I to ROHS III directives
- Raw material compliance data (USP standards)
- Packaging and packaging waste directive 94/62/EC
- System designed in accordance with the American Society of Civil Engineers (ASCE) 7 Minimum Design Loads and Associated Criteria for Buildings and Other Structures

The automation platform enables compliance with US FDA 21 CFR Part 11 environments and follows the GAMP 5 life cycle for software development.

System variants

The automation architecture is based on either Siemens S7 PLC or Rockwell CompactLogix PLC and a server PC. Two automation options are available:

- PLC (Rockwell or Siemens) and HMI for local stand-alone control
- Remote I/O (no PLC, HMI, or PC) for integration into a DCS or SCADA system

Specifications

Process specifications

Equipment	Specification
Functionality	Sterile filtration (drug product)
Number of pumps	2
Pump 1 (inlet pump) flow rate range	6 to 420 L/h (with Pumpsil tubing 12.7 mm i.d.)
Pump 2 (recovery pump) flow rate range	3.6 to 90 L/h
Number of inlets	2
Tube dimension inner diameter	0.5 inch
Flow path operating pressure	0 to 4 barg (dependent on the installed capsules)
Integrity test pressure	Dependent on the installed capsules
Flow path operating temperature range	4°C to 40°C
Filter	Air filter; Emflon™ II membrane in Kleenpak™ capsules KA1 (1× single filtration, 2× redundant filtration)
External connections	2× mixer (Phoenix), 2× temperature, 2× mixer (ethernet), 2× mixer E-stop (Phoenix), 3× weight scale (Harting), 1× flush bag trolley weight scale (Harting)

System specifications

System	Specification
Materials of construction	Stainless steel 1.4301 (304)
Surface finish	Cold rolled steel with minimal work marks (typically Ra < 1.2 µm)
Ingress protection rating	CE version: IP54 UL version: NEMA 4X for electrical cabinets only

Dimensions and weight

	Skid	Trolley 20 L	Trolley 50 L
Mass (kg)	600	135	205
Dimensions (W x H x D cm)	112 × 199 × 102	120 × 150 × 80	120 × 150 × 100

Utility specifications

Utilities	Specification
Process air	6 barg minimum.
Instrument air	Recommended 6 to 7 barg. 10 barg maximum. Instrument air, clean, dry and oil free
Electrical supply	230 VAC – 50 Hz (CE) 240 VAC – 60 Hz (UL)

Ordering information

To order the drug product filtration system, please contact your local Cytiva sales representative.

Description	Product code
Drug product filtration system UL	31169286
Drug product filtration system CE	31169287
Drug product filtration system CE I/O	31169302
Drug product filtration system UL I/O	31169323
Flush trolley with scale for 20 L flush bag	31170039
Flush trolley with scale for 50 L flush bag	31170040

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