

TITLE OF THE INVENTION

Hierarchical Closed-Loop Micro-Dosing Skid with Multi-Axis Gear-Pump Manifold and Optional Disposable Cartridges

DESCRIPTION

[0001] FIELD

The invention relates to automated bioprocess control systems and, more specifically, to skid-mounted equipment that delivers sub-microlitre reagent doses into plasma-fractionation, viral-clearance, formulation and cell-culture streams under real-time process-analytical feedback—using a multi-axis positive-displacement pump manifold optionally combined with single-use reagent cartridges.

[0002] BACKGROUND

In plasma-derived therapeutics, viral-vector manufacture, monoclonal-antibody purification, and advanced cell-therapy cultures, trace reagents (e.g., low-pH virus-clarifiers, endotoxin binders, surfactants, antioxidants, cryoprotectants, cytokines, and nucleases) are often added in sub-microlitre increments to tens-of-litre process streams. Historically these additions have been made (i) manually from bench stock, (ii) by time-based diaphragm pumps that lack real-time feedback, or (iii) via fixed single-use cartridges that passively release reagent as the bulk stream flows through them. These approaches suffer several drawbacks:

- **Poor dose precision at litre-scale flow rates.** Conventional positive-displacement pumps struggle to deliver repeatable pulses below 10 μL ; passive cartridges cannot adjust dose rate at all.
- **Lack of real-time process control.** Temperature, pH, redox, dissolved gas, viral titre, and endotoxin levels frequently drift outside the design space before manual sampling or feedback can occur, leading to rework or batch discard.
- **Incompatibility with harsh solvents and steam sterilisation.** Ethanol concentrations above 40 % v/v and SIP requirements $> 121\text{ }^\circ\text{C}$ quickly embrittle or warp many polymer housings used in single-use hardware.

- **Traceability gaps.** When multiple reagent lanes merge upstream of a sensor, electronic batch records cannot unambiguously link each corrective action to a specific pump or cartridge lane, complicating deviation investigations and continued-process-verification (CPV) reporting.
- **Consumable cost and waste.** Radial cartridge banks often require twenty-plus single-use housings per batch, adding material cost and generating regulated bio-hazard waste.

Attempts to improve accuracy by splitting a bulk pump into parallel flow-paths or by shrinking diaphragm-pump stroke volumes have delivered limited success; flow splitting introduces pulse dampening and variable back-pressure, while micro-strokes exacerbate check-valve hysteresis and wear. Fully disposable skid assemblies overcome solvent and sterilisation limitations only at the expense of higher consumables cost and environmental load.

Therefore, a need exists for a reagent-delivery architecture that (i) achieves $< 1\%$ coefficient-of-variation at $\leq 1\ \mu\text{L}$ dose volumes, (ii) couples each dose to a real-time process-analytical-technology (PAT) signal, (iii) withstands aggressive solvents and steam-in-place cycles, (iv) records lane-by-lane genealogy for 21 CFR § 11 and EU Annex 11 compliance, and (v) preserves the flexibility of single-use chemistry where solid-phase or sterile disposability is essential.

[0003] SUMMARY

Disclosed is a reagent-delivery module comprising:

1. **A rack of $N=21$ micro-annular gear pumps** ($\leq 6\ \text{mL min}^{-1}$ each) whose pump heads and rotors are fabricated from 316L stainless steel and PEEK, magnetically coupled to servo drives on an EtherCAT field-bus.
2. **A sanitary injection ring** having twenty-one radial quills ($\text{ID} \leq 1.6\ \text{mm}$) merging into a common aseptic tee, such that the coefficient of variation (CV) of a $5\ \mu\text{L}$ shot is $\leq 1\%$.
3. **A PAT spool** directly downstream housing (i) a quartz-crystal micro-balance with dissipation (QCM-D), (ii) a micro-LAL endotoxin cell, and (iii) a redox probe; these signals feed a real-time TwinCAT function block (*FB_PUMP_DOSE*).
4. **CIP/SIP architecture** wherein the pump wet-ends form part of the SIP loop, validated for 30 min @ $130\ ^\circ\text{C}$ without disassembly.
5. **Dynamic lane assignment logic** enabling any pump to dispense any one of k reagents, with reagent identity, volume ($\pm 0.05\%$), lot and time-stamp stored as a `LINEAGE_ID = BatchID#PumpID` within an ISA-95 level-3 historian.

Representative embodiments

Embodiment 1: The manifold of claim 1 wherein at least one pump is reassigned in-process from virus-clearance reagent to endotoxin binder without CIP by flushing $\leq 50\ \mu\text{L}$ WFI and verifying zero carry-over on the QCM-D signal.

Embodiment 2: The controller auto-learns the Jacobian $\partial(\text{sensor})/\partial(\text{dose})$ within a μ -band stored in non-volatile pump EEPROM, shrinking said μ -band by 25% once the 95% confidence interval of the Jacobian row falls below 10%.

Embodiment 3: Where the injection ring is jacketed for $-20\ ^\circ\text{C}$ operation and includes a dedicated mini-steam “jumper” loop to enable ring sterilisation independent of the main feed line.

Embodiment 4: Integration with a higher-tier **Vital-Override (VO)** that pauses all 21 axes if μLAL endotoxin $> 0.05\ \text{EU mL}^{-1}$, thereby guaranteeing pathogen safety while preserving learning data for lower **Quality-Critical (QC)** and **Yield-Optimiser (YO)** loops.

Advantages over prior filing

- EtOH compatibility to 100 % v/v;
- Reagent CV <1 % at $\leq 5 \mu\text{L}$;
- No consumable waste;
- Lane-specific genealogy compliant with EU Annex 11 and 21 CFR §11.

Optional disposable variant

The gear-pump ports may accept luer-lock micro-cartridges pre-filled with reagent to combine the advantages of sterile disposability with positive-displacement accuracy.

Alternative pump class

In another embodiment the positive-displacement micro-pumps are piezo-electric diaphragm pumps of $\leq 2 \mu\text{L}$ stroke volume having identical EtherCAT control framing.”

Fail-safe & redundancy

A watchdog task disables all axes if two consecutive sensor packets are missed or if dose variance exceeds three standard deviations.

Calibration & self-test

Each shift, the controller executes an auto-prime delivering 25 μL WFI; QCM-D verifies zero carry-over ($\Delta f < 2 \text{ Hz}$) before unlocking recipe execution

Predictive-maintenance hook

Running hours and valve cycles are written to the historian; a LightGBM model predicts seal wear and schedules maintenance when predicted CV drifts by $>0.2 \%$.

MES / OPC-UA interoperability

Dose events and PAT spectra are exposed via an OPC-UA server node; native ISA-95 B2MML messages permit direct MES ingestion.

Scalability statement

The manifold scales by mounting additional racks and enlarging the injection ring diameter; preserving CV by proportionally adjusting quill ID ($\leq 2.0 \text{ mm}$).

Optional dual-ring architecture

A dual-ring variant routes odd-numbered pumps to an inner ring and even-numbered pumps to an outer ring, permitting simultaneous EtOH and aqueous micro-dosing.”

Best-mode disclosure (§ 1.132)

Best mode presently contemplates HNP mzt-4622 pumps with 1.5-Nm servos, 316 L ring ID = 38 mm, quill ID = 1.4 mm, and PAT spool length of 110 mm.”

Industrial applicability (PCT Rule 5.6)

The device is applicable in the manufacture of immunoglobulin concentrates, viral vectors, monoclonal antibodies, and adoptive-cell therapies.”

The skid operates from –25 °C to +40 °C ambient and is useful for IgG, AAV, mAb and CAR-T manufacture.”

Environmental spec

System operates between –25 °C and +40 °C ambient, 10–95 % RH non-condensing.

[0004] BRIEF DESCRIPTION OF DRAWINGS (placeholders)

Figure No.	Title & Short Description
FIG. 1	System Block Diagram – Illustrates reagent reservoirs, the 21-pump rack, sanitary injection ring, PAT spool, controller, and downstream process line.
FIG. 2	Control-Logic Flowchart – Three-tier hierarchy (Vital-Override → Quality-Critical → Yield-Optimiser) with decision diamonds and pump-dose actions.
FIG. 3	Micro-Annular Gear Pump Cross-Section – Shows annular gear (132), spur gear (138), housing (120), magnetic coupling and shaft seals (136).
FIG. 4	Injection-Ring Cross-Section – Perspective cut-away of 316 L ring with radial quill (212) and CIP jumper loop.

FIG. 5 PAT Spool Detail – Enlarged axial section depicting quartz-crystal micro-balance, micro-LAL flow-cell, ORP probe port and steam drain (not yet drawn—line drawing to be added).

FIG. 6 Optional Disposable Micro-Cartridge – Luer-lock insert with reagent cavity, burst seal diaphragm and RFID puck (reserve for cartridge variant claims).

FIG. 7A Exploded Isometric of 21-Pump Rack & Injection Ring – Overall assembly with numbered reference parts, steam jumper loop, and EtherCAT drive bay.

FIG. 7B Dual-Ring Scalable Variant – Diagram showing inner/outer injection rings for simultaneous EtOH and aqueous dosing (optional embodiment for continuation claims).

[0005] With reference to FIG. 1, reagent reservoirs 12 supply individual micro-annular gear pumps 14 mounted in rack 16. Discharge ports of the pumps communicate through lines 18 to sanitary injection ring 20, which in turn feeds the process line 22 leading to the downstream unit operation (not shown). A PAT spool 30 is positioned directly downstream of the ring and transmits real-time sensor values to programmable controller 40, which in turn issues drive commands to the respective pumps 14 in accordance with the control logic of FIG. 2.

[0006] Turning to FIG. 5, the PAT spool 30 houses a quartz-crystal micro-balance 52, a micro-LAL flow cell 54, and an oxidation-reduction-potential (ORP) probe port 56; a steam drain 58 enables complete sterilant removal during SIP. The controller records each micro-dose together with the corresponding sensor response, thereby generating a lineage entry (batchID|pumpID|reagentID|time-stamp) for every correction event.

[0007] As depicted in FIG. 6, an optional disposable micro-cartridge 60 may be attached to the injection ring via a luer-lock insert 62. A burst-seal diaphragm 64 isolates the pre-filled reagent cavity 66 until initialisation; an RFID puck 68 stores cartridge lot, sterility and expiration data. When the controller selects a cartridge lane, the diaphragm 64 ruptures and the micro-dosing pump meters reagent through the cavity 66 without altering the hierarchical VO/QC/YO algorithm described above.