[0009] CLAIMS

Claim Set I – Apparatus

1. **An automated reagent-dosing skid** comprising:
   a. a rack supporting *N* independently driven positive-displacement micro-pumps, each micro-pump having a suction port and a discharge port;
   b. a plurality of reagent reservoirs, each fluidly connected to at least one suction port and configured to be identified by machine-readable media;
   c. a sanitary injection ring having *N* radial inlet quills connected respectively to the discharge ports of the *N* micro-pumps;
   d. at least one in-line process-analytical sensor positioned downstream of the injection ring and producing a signal representative of a process parameter; and
   e. a programmable controller that, responsive to the signal, actuates an associated one of the *N* micro-pumps to deliver a corrective micro-dose of reagent while recording a traceable event that includes batch identity, pump identity, reagent identity, dose volume and time-stamp.
2. The skid of claim 1 wherein each micro-pump is a micro-annular gear pump capable of dispensing pulses of ≤1 µL with a coefficient of variation of ≤1 percent.
3. The skid of claim 1 wherein *N* equals twenty-one.
4. The skid of claim 1 further comprising a steam-in-place jumper loop that sterilises the injection ring and the micro-pumps without disassembly for at least thirty minutes at a temperature of 130 °C.
5. The skid of claim 1 wherein the controller executes a hierarchical algorithm comprising:
   (i) a Vital-Override tier that, upon detection of a safety-related excursion, suspends all lower tiers;
   (ii) a Quality-Critical tier that maintains a validated design space; and
   (iii) a Yield-Optimiser tier that adjusts reagent usage to maximise process yield.
6. The skid of claim 1 wherein the machine-readable media comprise radio-frequency identification (RFID) tags that store at least reagent lot and expiration data.
7. The skid of claim 1 wherein the process-analytical sensor is selected from the group consisting of: a quartz-crystal micro-balance with dissipation, a micro-LAL endotoxin cell, a near-infra-red ethanol probe, an oxidation-reduction potential probe, and a toroidal conductivity probe.
8. The skid of claim 1 further comprising at least one disposable cartridge positioned downstream of the injection ring, the cartridge containing a solid-phase or liquid reagent selected from the group consisting of: a virus-clarification medium, an endotoxin-binding resin, a nuclease coil, and a surfactant stripping bed.
9. The skid of claim 8 wherein the controller doses a first reagent directly through the injection ring and doses a second reagent into the disposable cartridge without altering the hierarchical algorithm of claim 5.
10. The skid of claim 1 wherein the event recorded by the controller is stored in an electronic batch record as a lineage identifier comprising a concatenation of batch identification, pump identification and reagent identification.

Claim Set II – Method

11. **A method of closed-loop reagent delivery to a bioprocess stream** comprising the steps of:
    a. providing a skid according to claim 1;
    b. measuring, with the at least one process-analytical sensor, a process parameter of the bioprocess stream;
    c. determining, in real time, a deviation of the process parameter from a set-point;
    d. actuating a selected one of the *N* micro-pumps to deliver a micro-dose of reagent through the injection ring sufficient to reduce the deviation; and
    e. logging, for each micro-dose, batch identity, pump identity, reagent identity, dose volume and time-stamp in a computer-readable medium.
12. The method of claim 11 wherein the deviation is an endotoxin concentration exceeding 0.05 EU mL^{-1} and the micro-dose comprises an endotoxin-binding polycation.
13. The method of claim 11 wherein the deviation is an ethanol concentration error of greater than ±0.5 percent v/v and the micro-dose comprises 96 percent ethanol delivered by a first micro-pump.
14. The method of claim 11 further comprising suspending all micro-pumps except a micro-pump associated with a Vital-Override tier when the process parameter exceeds a safety limit.
15. The method of claim 11 further comprising steam-sterilising, in situ, the injection ring and the *N* micro-pumps for at least thirty minutes at 130 °C without removing any wetted components.

Claim Set III – Computer-Read-Media

16. A non-transitory computer-readable medium storing instructions that, when executed by a processor, cause the processor to perform the steps of the method of claim 11.

17. **A bioprocessing system** comprising:
    a. the automated reagent-dosing skid of claim 1;
    b. a process vessel fluidly coupled to the injection ring, the process vessel holding a bioprocess stream selected from the group consisting of a plasma-fractionation intermediate, a viral-vector harvest, a monoclonal-antibody solution and a cell-culture bulk; and
    c. downstream clarification or filtration hardware selected from the group consisting of an ultrafiltration/diafiltration module, a virus-removal filter and a bulk-fill manifold,
    wherein the programmable controller of the skid communicates with a supervisory control system to coordinate reagent dosing with flow rate set-points of the process vessel and the downstream hardware.
18. The system of claim 17 further comprising an upstream reservoir supplying ethanol or buffer to the process vessel, the upstream reservoir being equipped with a level sensor that provides a signal to the programmable controller of the skid to anticipate solvent-curve changes.

19. The system of claim 17 wherein the process vessel is a jacketed cold-ethanol precipitation tank operated at −20 °C, and the programmable controller doses ethanol through the injection ring to maintain solvent concentration within ±0.5 percent v/v of a target profile.
20. The system of claim 17 further comprising at least one disposable cartridge positioned between the injection ring and the downstream hardware, the cartridge containing a virus-clarification medium that provides ≥6-log10 viral-reduction factor when the skid doses a low-pH reagent through the injection ring.
21. The system of claim 17 wherein odd-numbered pumps are fluidly connected to an outer injection ring that carries an aqueous reagent and even-numbered pumps are fluidly connected to an inner injection ring that carries an organic solvent, thereby enabling simultaneous solvent and aqueous micro-dosing without cross-contamination.
22. The system of claim 17 wherein the programmable controller receives a Vital-Override signal from an endotoxin sensor located in the downstream hardware and, upon receiving the signal, suspends dosing of all reagents except an endotoxin-binding polycation until the endotoxin level falls below 0.05 EU mL⁻¹.
23. The system of claim 17 wherein the supervisory control system records, for each batch, a data set comprising pump-dose lineage identifiers, process-analytical measurements and filtration differential pressures, the data set being stored in a 21 CFR § 11-compliant electronic batch record.

24. The skid of claim 1 wherein each micro-pump is a piezo-electric diaphragm pump having a stroke volume ≤ 2 µL.

26. The medium of claim 16 further comprising instructions to predict seal wear based on cumulative dosing variance and to issue a maintenance alert when predicted CV drift exceeds 0.2 %.”