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JAVITS CENTER, NYC
EXPERIENCE SCIENCE THROUGH COMMERCIALIZATION

Improving WFI Point-of-use with single-use flow control

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The Current State

We'll review:

- What the industry currently looks like
- Current industry workflows that are ripe for streamlining (e.g. the problem statement)

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WFI Infrastructure in Single-Use Facilities - ATMP Facility

Unit Operation	Gal. Usage	GPM flow	Frequency
Dirty parts staging	20	2	1x / day
Microfluidizer	793	7	1x / 2 wks
Depth filtration	528	4	1x / 2 wks
Chrom A / B	132	9	1x / 2 wks
Viral Filtration	26	3	1x / 2 wks
UF/DF	26	3	1x / 2 wks
2000 L SUM	528	12	1x / day
500 L SUM	132	9	2x / day
200 L SUM	52	4	2x / day
Autoclave A	8	15	1x / day
Autoclave B	8	15	6x / day
Parts washer	50	5	1x / day
Tote washer	100	10	1x / day
Janitor's closet A / B	20	4	1x / day
Solution prep	52	4	3x /day

ATMP model:

- 122,000 ft^2 facility
- 8 cell therapy products
- 2 gene therapy products
- Assumes: Stainless WFI Generation and Distribution

WFI Infrastructure in Single-Use Facilities - Oligonucleotide Facility

Unit Operation	Gal. Usage	GPM flow	Frequency
Chrom A	52	7	1x / wk
Chrom B	132	8	1x / wk
Chrom C	52	10	1x / wk
Chrom D	52	7	1x / wk
Chrom E	52	7	1x / wk
UF/DF A	156	18	1x / wk
UF/DF B	26	18	1x / wk
UF/DF C	26	18	1x / wk
Lyophilizer A	793	40	1x / wk
Lyophilizer B	132	40	1x / wk
Lyophilizer C	132	5	1x / wk
Mixing vessel	528	5	1x /day
Prep vessel A	528	5	1x /day
Prep vessel B	4000	30	1x / wk
Prep vessel C	793	10	1x /day
Prep vessel D	793	10	1x /day
CIP skid	660	30	1x /day

Oligonucleotide model:

- 82,000 ft^2 facility
- 1 sense strand per train, per week
- 1 anti-sense strand per train, per week
- Assumes: Stainless WFI Generation and Distribution

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WFI Point of Use Workflow – Current State

Resource Requirements

WFI Consumption

• ATMP Example	1,435 gallons/day	358,732 gallons/year
• Oligonucleotide Example	4,103 gallons/day	1,025,679 gallons/year.

Square Footage

- Approx 25 sq ft per floor (w/ scale)
- Additional bag holders for mobility / flexibility
- Hold bags required for intermediate steps - (e.g. buffer, WFI)

Additional Considerations

- Delivery, disposal, inventory
- Maintenance & calibration

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WFI Point of Use Workflow – Current State

Current Accepted Measurements

Scales and Load Cells:

- Mass Measurement.
- High performance / accurate.
- Ethernet enabled for ease of operations.
- Scales can be affected by uneven mass distribution.
- Load cells can require recalibration when moved.
- Load cell per bag holder or scale per use-point.

Radar Measurement

- Level measurement.
- Flexible; portable.
- Low maintenance (no reprogramming or calibrating).
- Application for smart instrument increases reliability of installation.
- Radar per bag holder or per use-point.

Innovation is Changing Needs for WFI

Continuous Manufacturing

- Reduced footprint needed for continuous manufacturing.
- efforts to make WFI “on-demand” accessible for flexible system needs.
- Demand for a reduction of hold bags and break steps.

New modalities

- Cell & Gene Therapies vary in raw material needs.
- Standardization of systems increases flexibility.
- Reduction of scales and bag holders optimizes square footage.
- CDMOs require flexibility to meet varying needs of clients.

The Solution

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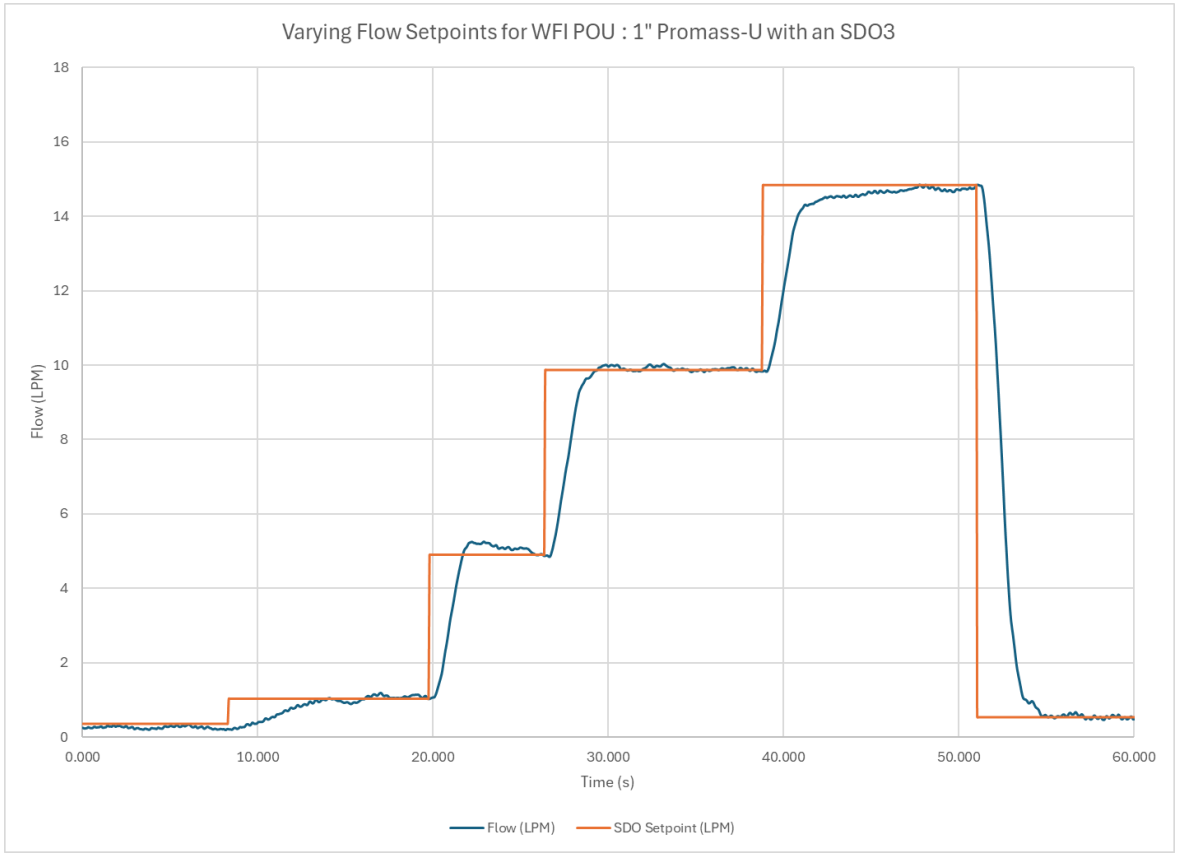
Flow Control Setup and Performance Expectations for POU

Components:

- Equilibar SDO Valve : SDO3NZA2-XXXXX
- Pilot Regulator : Industry standard 4-20 mA
- Endress & Hauser Flow Meter : 1” Promass U
- Control Loop : LabVIEW with 15 Hz loop rate



Performance:

- Exceeded low end control (0.3 LPM control demonstrated with low limit ~2.3 LPM for 1” Promass-U)
- Fast response to setpoints under varying WFI conditions
- 100:1 turndown capable, data presents >40:1

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Key Advantages & Benefits

- 100:1 turndown → 1 tube set size for all WFI flow needs
  - Oligonucleotide Example : 8:1 flow control turndown needed
  - ATMP Example : 7.5:1 flow control turndown needed
  - 20:1 overall to cover full flow ranges needed in both examples
- Reduced SKUs for plant maintenance / logistics
- Pulsation free dosing improves accuracy of Promass U
- Calibration verification provided by Promass U via Heartbeat technology
- Mobile configuration for improved clean room workflow

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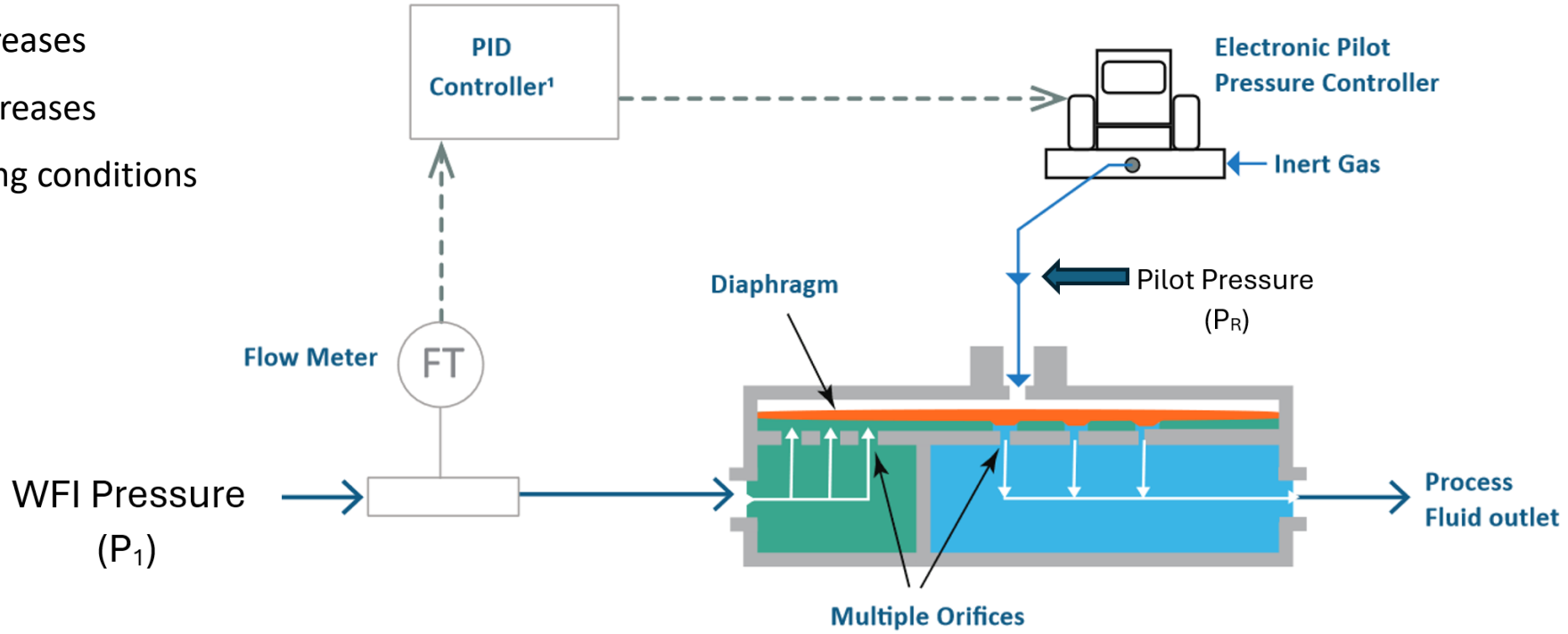
Flow Control for WFI POU - How does it work

- Incoming WFI establishes P_1
- Flow moves through the flow meter and a signal is generated
- PID controller compares flow value to setpoint and adjusts signal to the pilot regulator
- P_R pilot pressure is adjusted according to the condition
  - Flow > Setpoint, P_R increases
  - Flow < Setpoint, P_R decreases
  - $P_R \approx P_1$ at most operating conditions
  - To close, set $P_R > P_1$



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Endress+Hauser's Promass U - Single-Use Coriolis Flow Meter

Key characteristics	Specifications
Mass and volume flow accuracy liquids	±0.50% o.r.
Repeatability liquids	±0.25% o.r.
Flow range	⅛ to 1" (0.1 to 75 l/min)
Wetted parts materials	Tube: Stainless steel 1.4435 316L Flow splitter: Polycarbonate Makrolon Rx1805
cGMP calibration compliance	Factory calibrated with traceable Heartbeat Technology
Application fit	One base unit fits all line sizes
Handling	Simple, one-handed disposable installation Self-verification upon installation
Pharmaceutical compliance	ISO class 7 packaging, gamma sterilizable
Certification/approvals	cGMP, FDA, ASME BPE, BPOG, USP Class VI, TSE/BSE, 3.1
Communication * w. Ethernet-APL/SPE, 10Mbit/s, 2-wire	3 configurable I/O's (PFS, Relay, 4-20mA) Modbus RS485, Modbus TCP* or PROFINET*
One design fits 3 applications	Laboratory, process, OEM panel mounting

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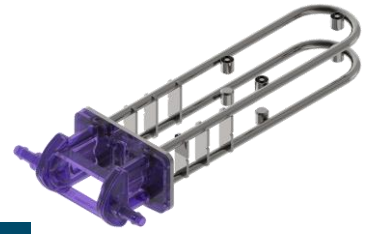
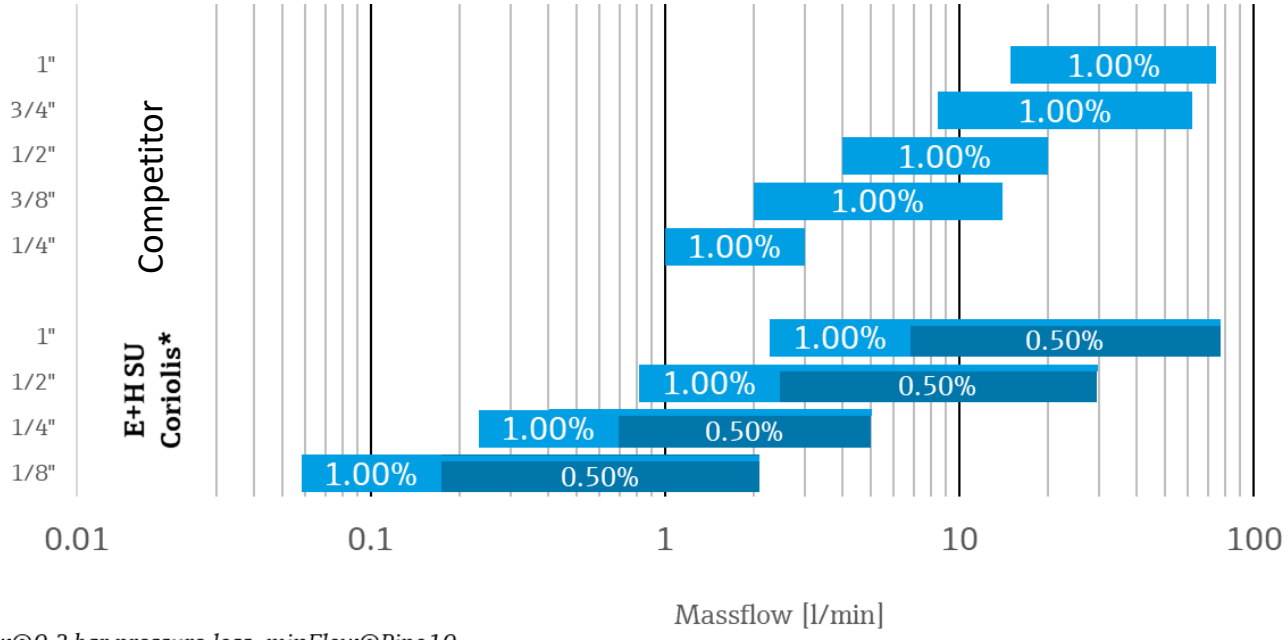
Promass U - Sensor



- One sensor for 4 line sizes *(1/8", ¼", ½" and 1")*
- Fully traceable calibration
- 0.5% accuracy
- Turn down 1:100 *(Min Flow up to 0.2 bar pressure loss)*



maxFlow@0.2 bar pressure loss, minFlow@Pipo10

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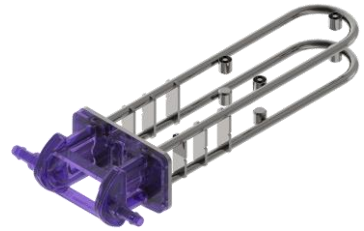
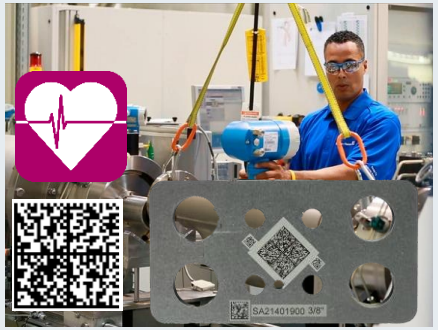
Verifying Factory Calibration



Uninterrupted and fully automated data trail
Heartbeat Technology automatically verifies the validation of the original factory calibration

Factory calibration

Heartbeat Technology data and calf are recorded and encoded on tube



Cleaning & tube assembly

Assembling with tubing and other components, cleaning, packaging, gamma sterilization

Installation on site

Installation of disposable assembly. Factory calibration and HBT data are automatically up-loaded to transmitter.

Commissioning:

1 - Verification

Heartbeat Verification is performed automatically after tube installation **to verify the validity of original factory calibration**.

On-site verification ? Factory calibration

2 - Zero Point Adjustment

Performed automatically to ensure highest measurement performance under process conditions

Production

Flowmeter is pre-calibrated and ready for cGMP operation

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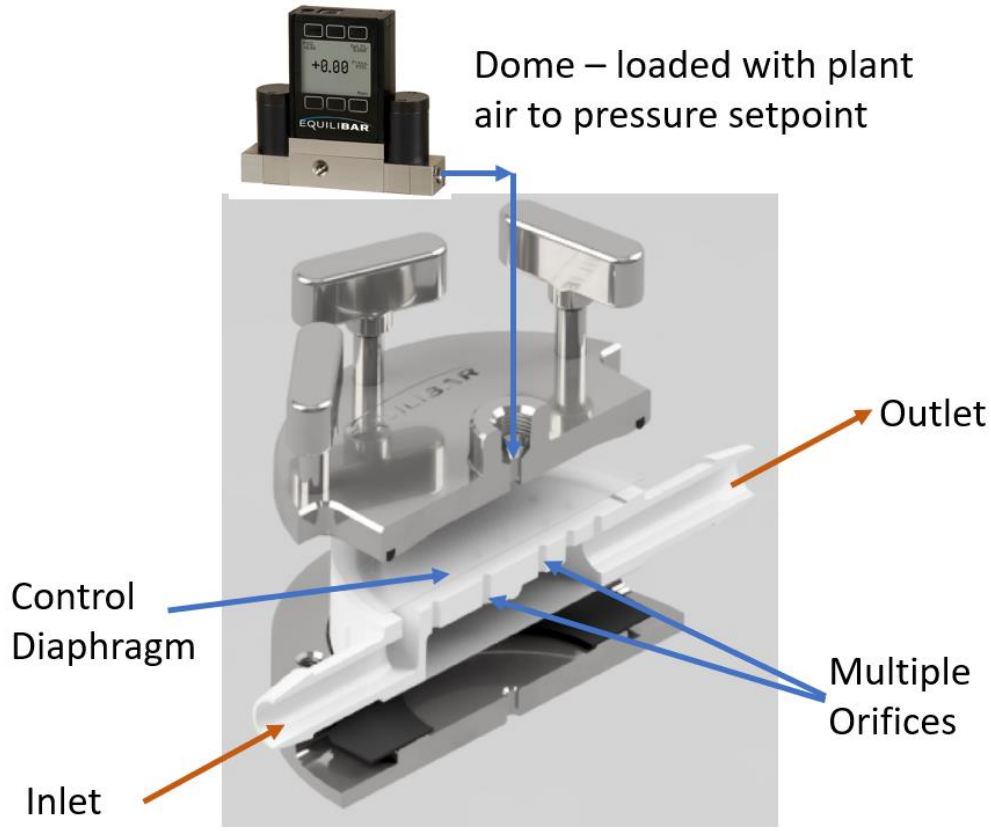
Equilibar's Singe-Use Pressure Regulator

Simple Design. Brilliant Control.

- Dome-loaded
- Diaphragm is the only moving part
- Multiple orifices
- 1,000:1 CV turndown TYP
- Pressure (TMP), Flow, pH, Conductivity (etc.) control
- Easy to automate
- cGMP capable
  - ISO Class 7 assembly, full certification package, 50 kGy gamma compatibility
  - 4 bar (60 psi) MAWP
  - Port Sizes : 1/8" – 1"



SDO Sanitary Regulator

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Typical Workflows Reimagined

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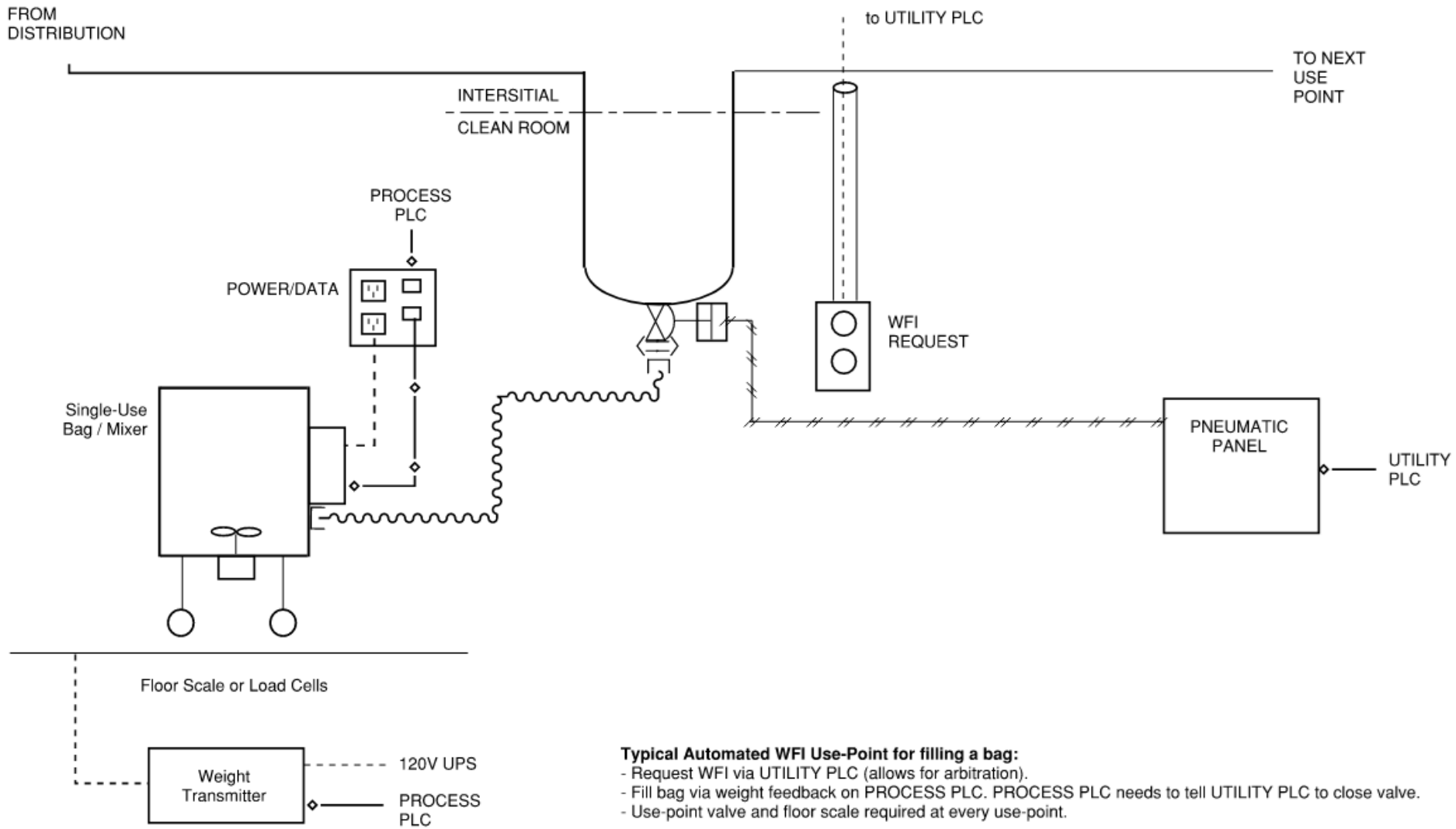
Use Case 1: Automated WFI Use-Point for filling a bag



Typical Automated WFI Use-Point for filling a bag:
- Request WFI via UTILITY PLC (allows for arbitration).
- Fill bag via weight feedback on PROCESS PLC. PROCESS PLC needs to tell UTILITY PLC to close valve.
- Use-point valve and floor scale required at every use-point.

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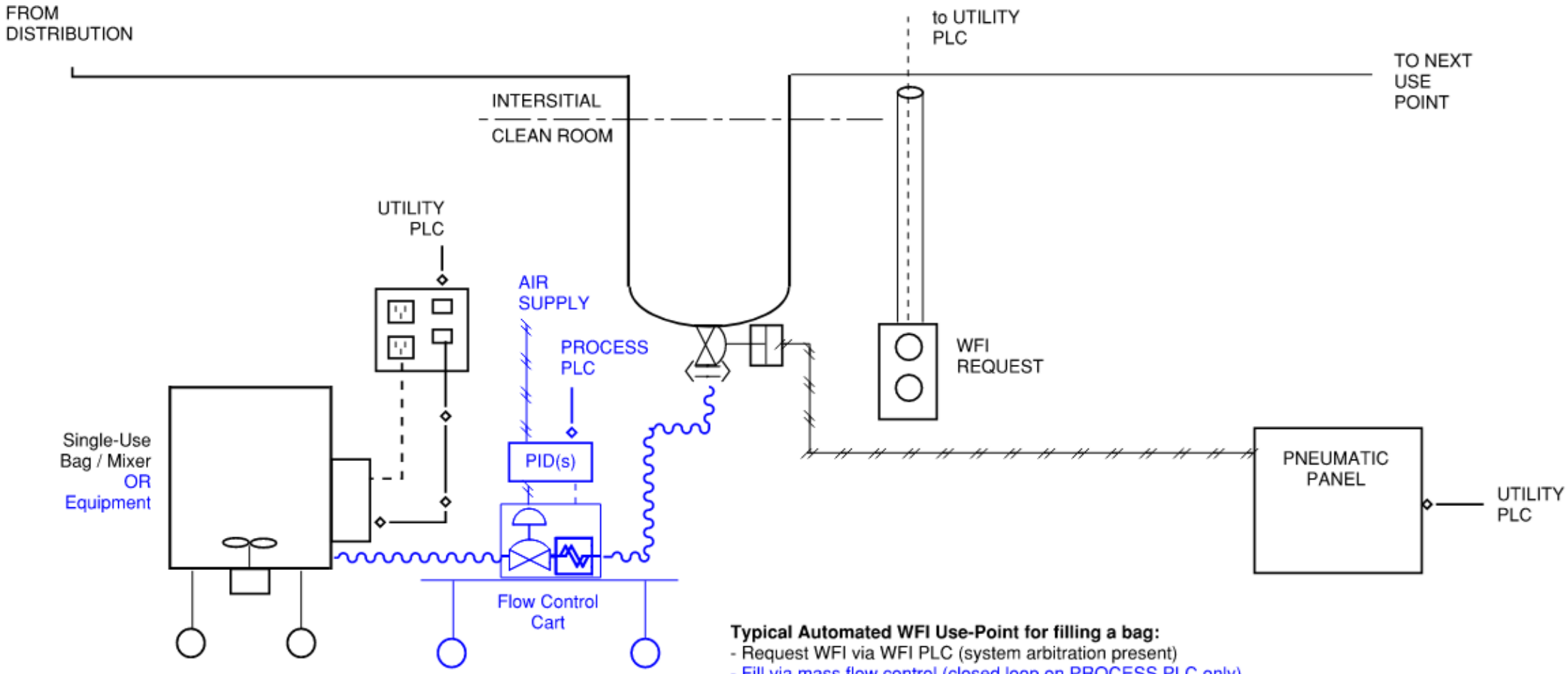
Use Case 1: Automated WFI Use-Point for filling a bag Reimagined



Typical Automated WFI Use-Point for filling a bag:

- Request WFI via WFI PLC (system arbitration present)
- Fill via mass flow control (closed loop on PROCESS PLC only)
- Control valve can shut off WFI supply without communication to UTILITY PLC.
- Portable flow control cart(s). No fixed scales.
- May be able to eliminate hold bag and directly connect to users.

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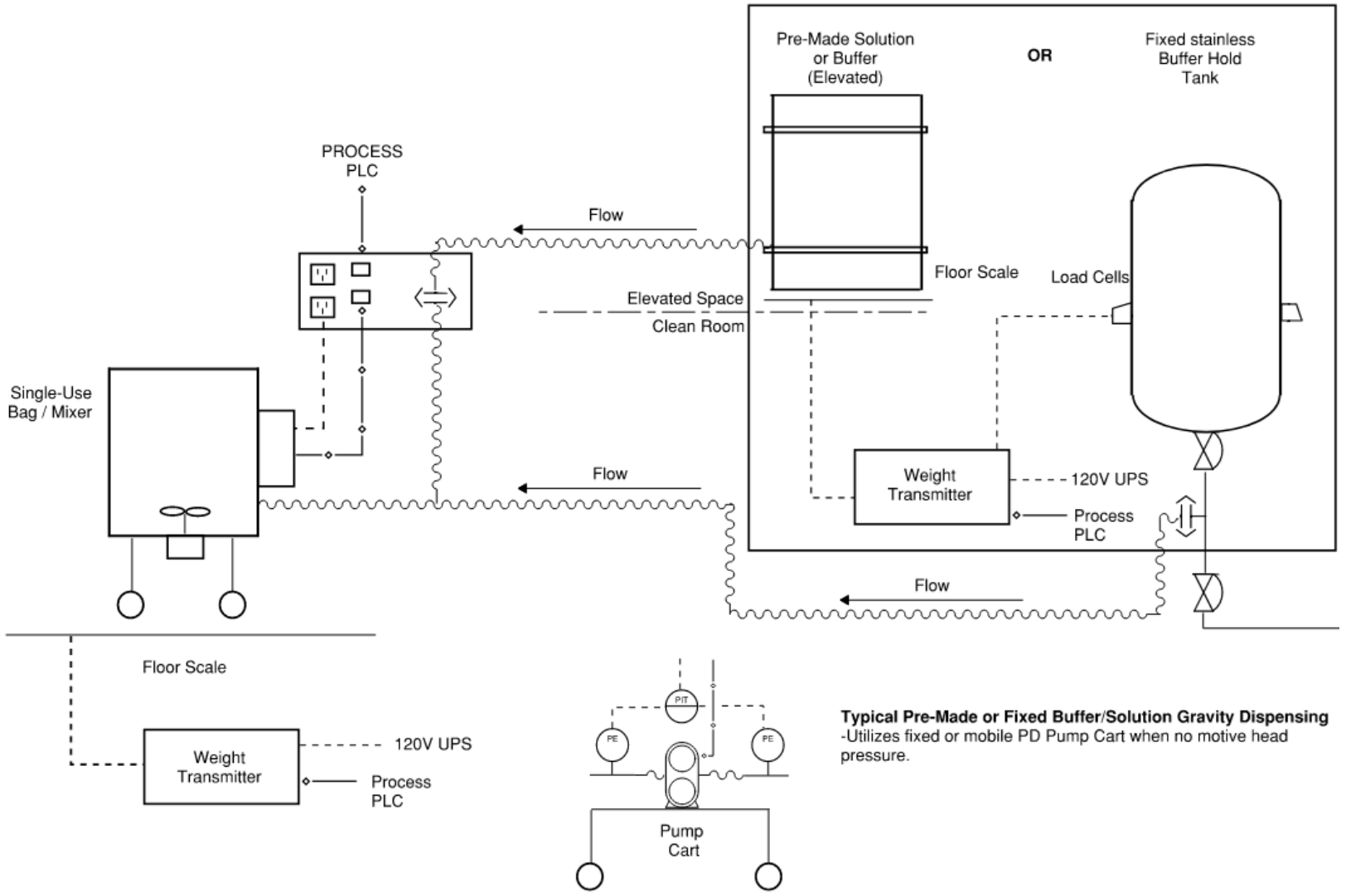
Use Case 2: Pre-Made or Fixed Buffer/Solution Dispensing



Typical Pre-Made or Fixed Buffer/Solution Gravity Dispensing
-Utilizes fixed or mobile PD Pump Cart when no motive head pressure.

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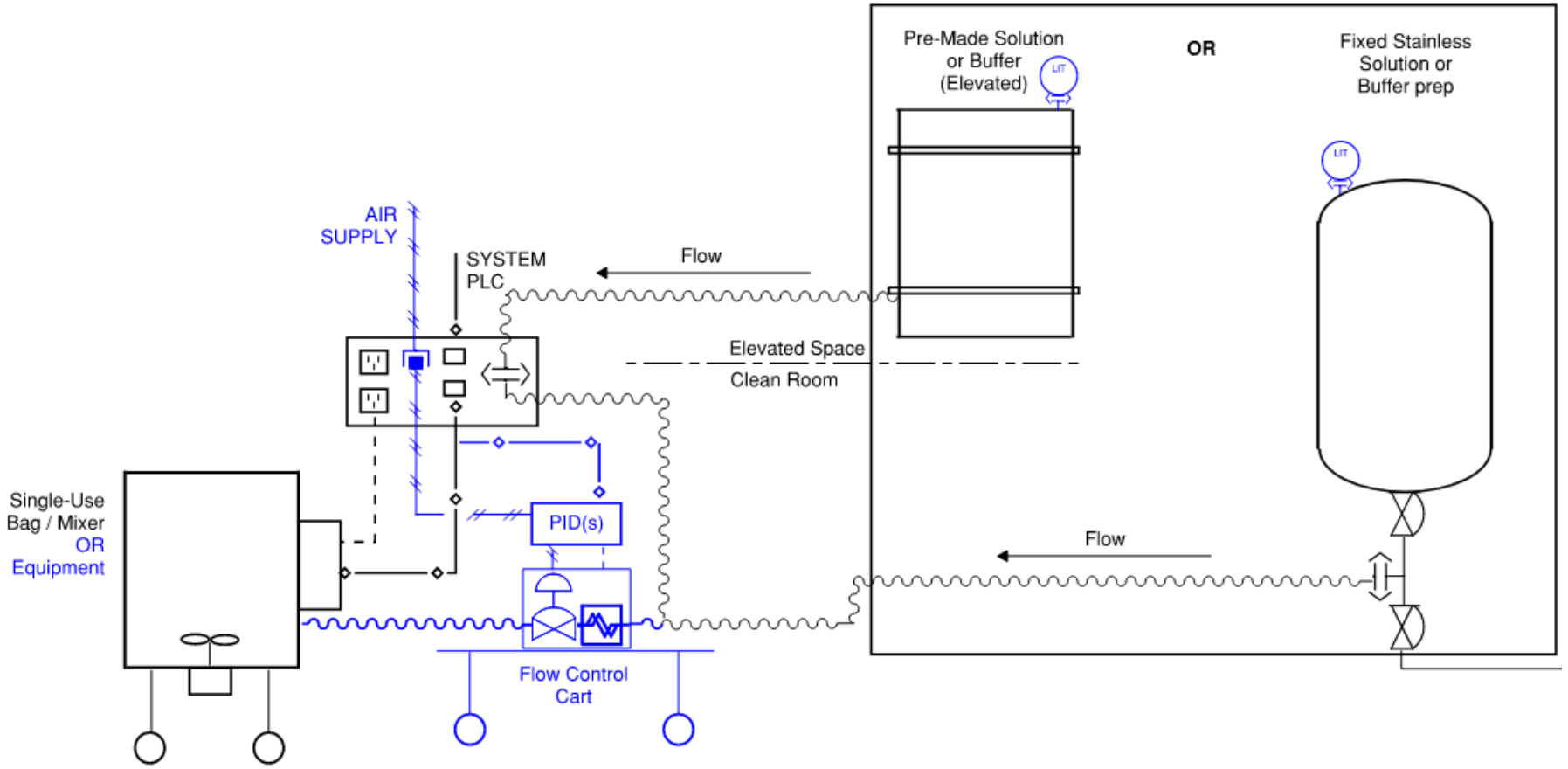
Use Case 2: Pre-Made or Fixed Buffer/Solution Dispensing Reimagined



Typical Pre-Made or Fixed Buffer/Solution Dispensing
-Eliminates need for scales at use-points.
-May eliminate need for load cells or scales for tanks / totes.
-Eliminates need for pump cart when head pressure is adequate.
- May be able to eliminate hold bag and directly connect to users.

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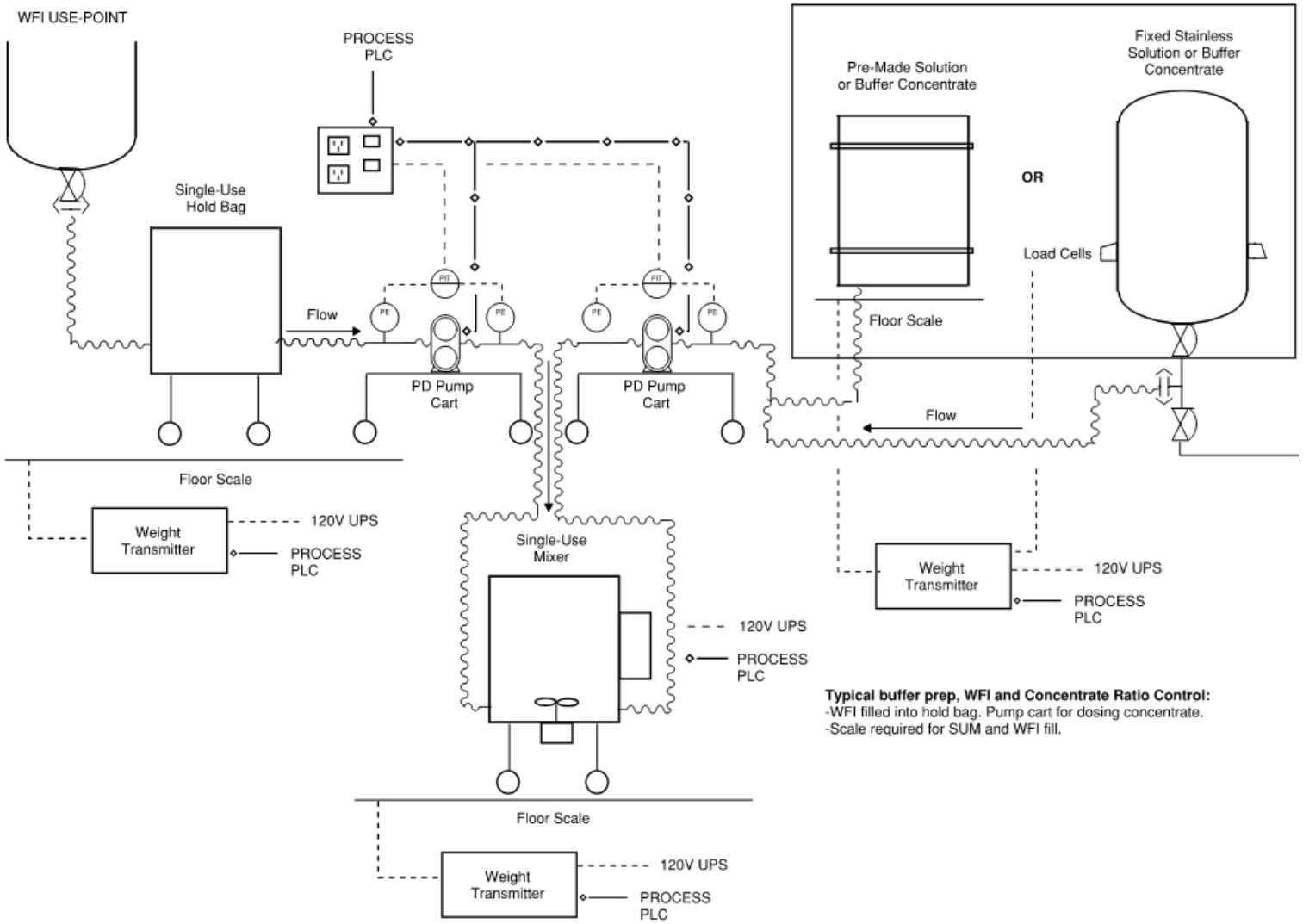
Use Case 3: Buffer Prep



Typical buffer prep, WFI and Concentrate Ratio Control:
-WFI filled into hold bag. Pump cart for dosing concentrate.
-Scale required for SUM and WFI fill.

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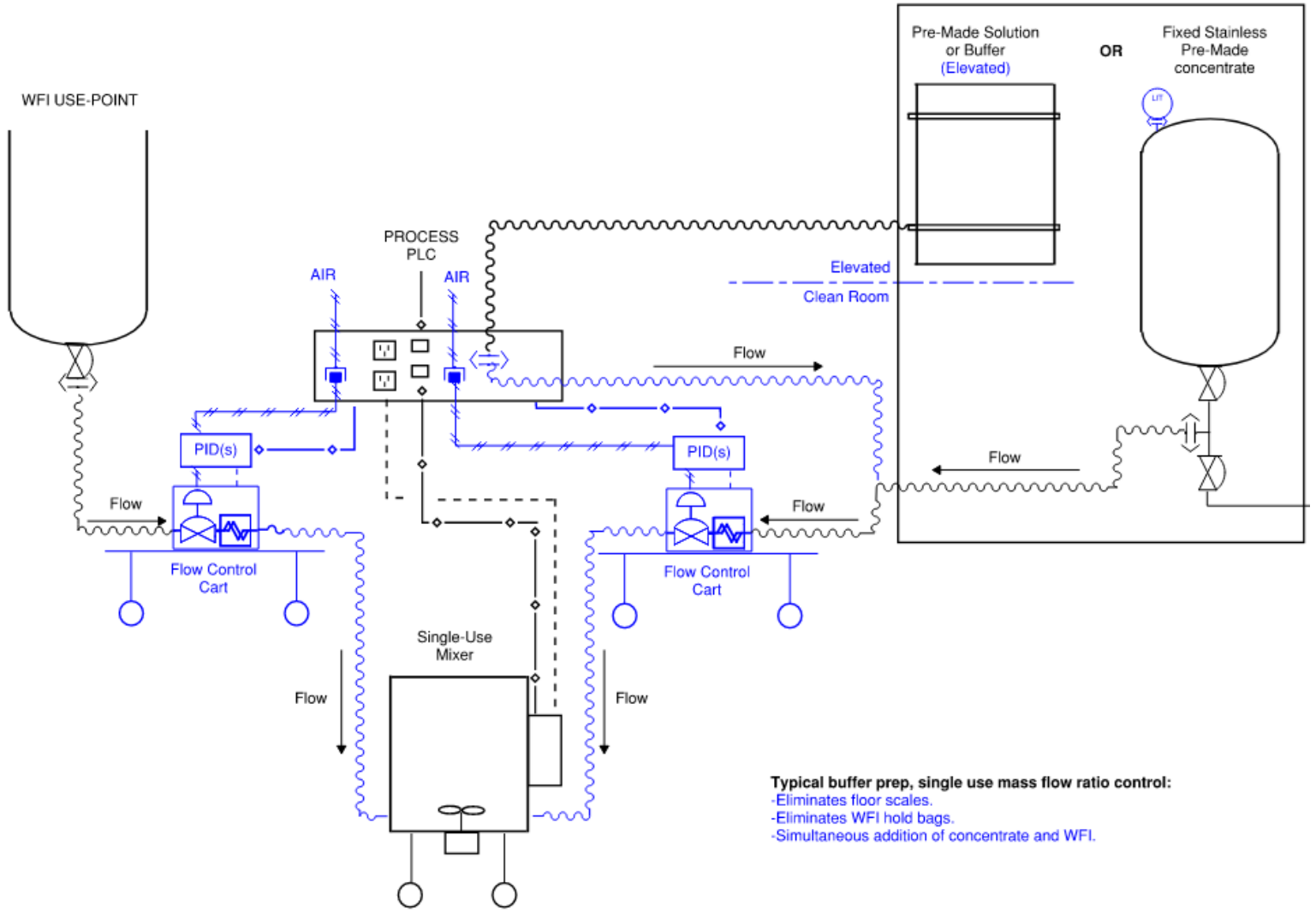
Use Case 3: Buffer Prep Reimagined



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Summary

- New modalities and methods require different needs for raw materials (WFI)
  - Turndown needed for two modalities studied is 20:1
- WFI POU access for flow control benefits:
  - Save 25 ft^2 per weigh scale
  - Improved accuracy of Promass-U flow meter with pulsation free flow control
  - Reduce labor cost for logistics and clean room personnel
- Flow Control requirements:
  - Equilibar SDO back pressure regulator
  - Endress & Hauser Promass-U flow meter
  - PID control
    - >20 Hz will provide best results

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Thank you!

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Visit us at our booths!

Equilibar Booth 2427 **Endress & Hauser Booth 2517** **Arcadis Booth 1861**

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