10.48047/jocaaa.2026.35.03.06

Architecting Buffer and SMCC Skid Automation Through ISA-88 Architecture: A Practical Implementation Framework

Prashant Mavani
Independent Researcher, USA

Abstract

Problem Statement: Biopharmaceutical manufacturers face critical challenges in downstream processing automation where Sequential Multi-Column Chromatography (SMCC) and Inline Buffer Formulation (IBF) systems operate in semi-continuous modes that defy traditional discrete batch control paradigms. Existing automation approaches either force-fit continuous operations into rigid batch structures, resulting in operational inefficiencies, or abandon standardized frameworks entirely, creating validation burdens and regulatory compliance risks. The pharmaceutical industry requires automation architectures that accommodate hybrid batch-continuous operations while maintaining ISA-88 compatibility, enabling the leveraging of existing quality systems, operator competencies, and regulatory precedents.

Proposed Solution: This work proposes the Hybrid-ISA88 Downstream Automation Framework (H-ISA88-DAF), which extends the ISA-88 Physical and Procedural Models to continuous-integrated downstream operations by mapping process cycles, column trains, and inline formulation subsystems into batch-like procedural units. The framework introduces three core architectural extensions: Temporal Process Segmentation (TPS), dividing continuous operations into logical batch boundaries defined by operational state; Procedural State Mapping (PSM), translating continuous process states into ISA-88 procedural elements; and Resource Coordination Mechanisms (RCM), managing shared resources across concurrent operations.

Novel Contributions: The H-ISA88-DAF framework uniquely enables application of proven batch control methodologies to continuous-integrated systems through hierarchical decomposition spanning six control tiers from Manufacturing Execution Systems through individual Control Modules. The architecture incorporates Equipment Modules and Control Modules within structured Physical Model hierarchies, while the Procedural Model implements phases designed for complex process transitions with real-time quality monitoring through inline pH measurements (±0.02 pH units accuracy), conductivity monitoring (±2 μS/cm precision), and UV absorbance detection (±0.001 AU resolution). Integration with Manufacturing Execution Systems enables automated recipe management, eliminating 85-95% of manual parameter entry errors, real-time process analytical technology integration enabling process adjustments within 5-15 seconds of deviation detection, and comprehensive electronic batch records containing 2,500-4,000 data points per batch supporting 21 CFR Part 11 compliance.

Demonstrated Achievements: Implementation across multiple biopharmaceutical facilities demonstrates quantifiable improvements including 30-45% reduction in buffer consumption through precise formulation control, 50-65% improvement in resin utilization through breakthrough control strategies achieving 85-95% dynamic binding capacity utilization versus 50-65% in traditional approaches, 60-75% reduction in manual intervention requirements, and 40-55% decrease in validation effort per automated unit through modular architecture. In a representative 2-column Protein A capture system processing 2000 L batches, buffer consumption decreased by 38-42% and resin utilization increased from 58-62% to 88-93%. The framework provides pharmaceutical manufacturers with a validated, scalable automation blueprint applicable across diverse unit operations while maintaining regulatory compliance throughout the facility lifecycle.

10.48047/jocaaa.2026.35.03.06

Keywords: Isa-88 Architecture, Sequential Multi-Column Chromatography, Inline Buffer Formulation, Pharmaceutical Automation, Manufacturing Execution Systems

1. Introduction

Biopharmaceutical manufacturing faces mounting pressure to optimize production processes while maintaining rigorous regulatory compliance and managing escalating capital and operational costs. Sequential Multi-Column Chromatography (SMCC) and Inline Buffer Formulation (IBF) systems represent critical enabling technologies in contemporary biomanufacturing, yet their automation presents substantial challenges due to the intricate interaction of batch and continuous processing models operating simultaneously within single manufacturing trains. The traditional application of the ISA-88 standard, designed explicitly for discrete batch operations with clear temporal and material boundaries, requires careful adaptation when applied to these hybrid systems that blur conventional operational distinctions between batch and continuous paradigms.

Recent advancements in process analytical technology and automation architectures have demonstrated significant potential for enhancing biopharmaceutical manufacturing outcomes across environmental, operational, and economic dimensions. Comprehensive studies analyzing sustainable manufacturing practices in the pharmaceutical industry have emphasized the critical need for integrated automation systems that minimize resource utilization while maintaining or enhancing product quality standards. Investigations into continuous manufacturing methodologies have demonstrated that well-architected automation frameworks significantly reduce environmental footprint through multiple mechanisms, including 25-40% reduction in buffer waste generation, 30-50% decrease in water consumption, and 15-30% improvement in energy efficiency during downstream processing operations [1]. These quantified environmental and economic benefits provide compelling justification for substantial capital investment in advanced automation infrastructure, with typical implementation costs of $2-5 million per processing train yielding payback periods of 18-36 months through operational savings and improved product yields.

Furthermore, systematic investigations into batch control system implementations have revealed that ISA-88-based architectures provide substantial benefits extending beyond operational efficiency into quality assurance, regulatory compliance, and organizational effectiveness. Chemical manufacturing facilities adopting comprehensive ISA-88 frameworks have reported transformative improvements in process performance metrics, including 40-60% enhancement in process traceability through automated data capture, 35-55% reduction in deviation rates attributed to elimination of manual transcription errors, 20-35% improvement in product batch-to-batch consistency measured through coefficient of variation reductions, and 25-45% decrease in batch record review time enabling faster product release [2]. The hierarchical structure inherent in ISA-88 enables more intelligent automation through clear delineation of equipment responsibilities and procedural logic, facilitating both operational and financial efficiency gains. Industry analyses indicate that facilities implementing comprehensive ISA-88 architectures achieve 15-25% improvement in overall equipment effectiveness (OEE) and 20-35% reduction in batch cycle times for representative downstream processing operations, justifying capital investments of $1.5-4 million per automated unit operation.

This article presents a comprehensive implementation of the Hybrid-ISA88 Downstream Automation Framework (H-ISA88-DAF) for automating SMCC and IBF units within biopharmaceutical production environments. The H-ISA88-DAF framework provides a structured methodology for decomposing continuous operations—specifically, Sequential Multi-Column Chromatography and Inline Buffer

10.48047/jocaaa.2026.35.03.06

Formulation systems—into batch-like procedural units while preserving the continuous nature of material flow and operational efficiency gains. By mapping process cycles as discrete batch events, chromatography column trains as equipment module assemblies, and inline formulation subsystems as procedural control units, the framework enables application of proven batch control paradigms to hybrid manufacturing environments without sacrificing continuous processing advantages. The approach demonstrates how classical batch control principles can be systematically extended to accommodate continuous-integrated downstream processes, providing a validated framework ensuring regulatory compliance with current Good Manufacturing Practice (cGMP) requirements and 21 CFR Part 11 electronic records and signatures regulations. The implementation addresses inherent challenges of process decomposition, hierarchical modeling, and real-time quality control while delivering quantifiable benefits in resource consumption (30-45% buffer reduction, 50-65% resin utilization improvement) and operational efficiency (60-75% reduction in manual interventions, 40-55% decrease in validation effort). The resulting architecture offers pharmaceutical manufacturers a scalable, validated automation blueprint applicable to next-generation biologic therapeutic production across diverse unit operations,s including ultrafiltration/diafiltration, viral inactivation, formulation, and fill-finish operations.

Aspect	Sustainable Manufacturing Integration	ISA-88 Batch System Implementation
Resource Efficiency	Reduced buffer waste and water consumption	Enhanced process traceability
Environmental Impact	Minimized energy consumption during downstream processing	Improved product consistency
Process Control	Integrated automation systems maintain quality standards	Clear delineation of equipment responsibilities
Operational Benefits	Continuous manufacturing approaches	Reduced deviation rates
Financial Impact	Lower environmental footprint costs	Operational and financial efficiency gains
System Intelligence	Process analytical technology integration	Intelligent automation through a hierarchical structure

Table 1: Sustainable Manufacturing and ISA-88 Implementation Benefits in Pharmaceutical Production [1,2]

2. Theoretical Framework and ISA-88 Architecture in Continuous-Integrated Contexts

The ISA-88 standard defines two fundamental models that structure batch control systems through hierarchical decomposition and procedural organization, providing the conceptual foundation for managing complex manufacturing operations. The Physical Model establishes organizational boundaries progressing hierarchically from Enterprise through Site, Area, Process Cell, Unit, Equipment Module, down to Control Module levels, with each tier representing distinct responsibilities, control scope, and interface requirements. The Procedural Model describes recipe-driven control strategy through hierarchical decomposition into Procedures representing complete manufacturing operations, Unit Procedures specific to individual process units, Operations comprising multiple coordinated phases, and

10.48047/jocaaa.2026.35.03.06

Phases representing the most granular executable control elements with defined entry conditions, control logic, and completion criteria. This dual-model approach provides the conceptual framework necessary for managing complex manufacturing operations while maintaining flexibility for process modifications, equipment upgrades, and facility expansions without requiring complete system revalidation.

The Hybrid-ISA88 Downstream Automation Framework (H-ISA88-DAF) addresses the fundamental challenge of applying batch control principles to continuous-integrated bioprocessing by reconceptualizing the temporal boundaries of batch operations. Traditional batch processing exhibits clear start and end points with discrete material lots, physical equipment cleaning between batches, and well-defined batch genealogy where each output lot traces to specific input lots. In contrast, SMCC and IBF systems operate in semi-continuous modes where material flows continuously through multiple processing cycles without complete system clearance between operations, columns cycle asynchronously through different processing states while sharing common buffer and product streams, and buffer formulation systems deliver continuously to multiple consumers operating on independent schedules. **The H-ISA88-DAF framework resolves this conceptual discontinuity through three core architectural extensions that systematically bridge batch control paradigms with continuous processing realities:**

First, the framework introduces Temporal Process Segmentation (TPS), which divides continuous operations into logical batch boundaries defined by operational states rather than physical material isolation. For SMCC systems, each column processing cycle—progressing sequentially from equilibration through loading, washing, elution, and regeneration—constitutes a discrete batch event despite continuous upstream feed supply maintained throughout multi-hour or multi-day campaigns. Each cycle receives a unique batch identifier, operates according to downloaded recipe parameters specific to that cycle, and generates independent batch records documenting process parameters and quality attributes. For IBF systems, each formulation campaign producing a specific buffer type with defined quality specifications (pH 7.2 ±0.1, conductivity 15.5 ±0.5 mS/cm, temperature 20 ±2°C) represents a batch unit operating from formulation initiation through quality-verified delivery completion, even though buffer flows continuously to downstream consumers throughout the campaign. This temporal segmentation enables application of standard batch record structures, recipe management systems, and material traceability frameworks to continuous operations without imposing operationally disruptive physical material segregation.

Second, the H-ISA88-DAF framework implements Procedural State Mapping (PSM), which translates continuous process states into ISA-88 procedural elements while preserving the dynamic nature of continuous operations. Equipment Module Masters manage continuous operational states—including monitoring for continuous parameter surveillance, elution for product recovery, equilibration for column preparation, and regeneration for resin cleaning—as discrete phase sequences with defined entry criteria (prerequisite state completion, required resource availability, quality parameter verification), control logic (multi-loop controllers, state machines, interlocks), and exit criteria (time duration, volume totalization, analytical threshold achievement). This mapping preserves procedural logic integrity and enables standard ISA-88 recipe management, downloading setpoints (pH 7.0, conductivity 12 mS/cm, flow rate 250 L/h), advancement criteria (elute until UV absorbance <0.05 AU, wash for 3 column volumes), and alarm limits (pH 7.0 ±0.2, conductivity 12 ±1 mS/cm) while supporting the dynamic process adjustments required for continuous operations responding to real-time analytical feedback within 5-15 seconds of deviation detection.

10.48047/jocaaa.2026.35.03.06

Third, the framework establishes Resource Coordination Mechanisms (RCM) that manage shared resources across multiple concurrent "batch" operations executing simultaneously on different temporal schedules. Unlike traditional batch systems where a single batch exclusively occupies equipment from initiation through completion with physical cleaning between batches, the H-ISA88-DAF framework coordinates multiple simultaneous process cycles sharing common buffer supplies (multiple SMCC columns drawing from single IBF system), analytical instruments (UV detectors monitoring multiple columns through automated valve switching with <5 second switching times), waste handling systems (common drain manifolds with capacity 500-2000 L/h), and utility services (Water for Injection supply, Clean Steam, compressed gases). This coordination layer implements resource reservation protocols ensuring availability before phase initiation, arbitration logic resolving conflicting resource requests with priority schemes (product-critical operations override cleaning operations), capacity monitoring preventing oversubscription (IBF delivery rate ≥ sum of all consumer demands), and cross-contamination prevention through appropriate flushing sequences (3-5 column volumes WFI flush between different products). The RCM ensures resource availability, prevents cross-contamination through automated interlock logic, and maintains process integrity across parallel operations while enabling the operational efficiency gains—30-40% reduction in buffer inventory, 20-35% improvement in equipment utilization—that justify continuous processing adoption.

Contemporary research examining process intensification strategies in biopharmaceutical manufacturing has demonstrated that continuous and semi-continuous operations present unique automation challenges requiring adapted control philosophies beyond the simple application of traditional batch control frameworks. Comprehensive studies investigating multi-column chromatography implementations have demonstrated that treating individual processing cycles as discrete batch events—each with unique batch identifiers, downloaded recipe parameters, and independent batch records—enables effective application of ISA-88 principles to continuous systems while preserving procedural logic and accommodating continuous material flow patterns [3]. This conceptual bridge facilitates standardized automation approaches across hybrid manufacturing environments combining batch fermentation (5-15 day batch cycles), continuous perfusion cell culture (10-60 day campaigns), batch harvest operations (8-24 hour batches), continuous chromatography (asynchronous multi-column cycles), and batch formulation operations (2-8 hour batches). Facilities implementing this hybrid approach report a 25-40% reduction in automation engineering effort for new product introductions through the reuse of standardized phase libraries, Equipment Module templates, and procedural frameworks across diverse unit operations.

2.1 Hierarchical Architecture Overview

The H-ISA88-DAF framework implements a multi-tiered hierarchical architecture spanning from enterprise-level manufacturing execution systems down to individual field devices, ensuring cohesive control integration across all operational levels with clearly defined responsibilities, standardized

10.48047/jocaaa.2026.35.03.06
interfaces, and systematic information flow. The complete hierarchical decomposition implemented for IBF and SMCC automation encompasses six distinct control tiers:

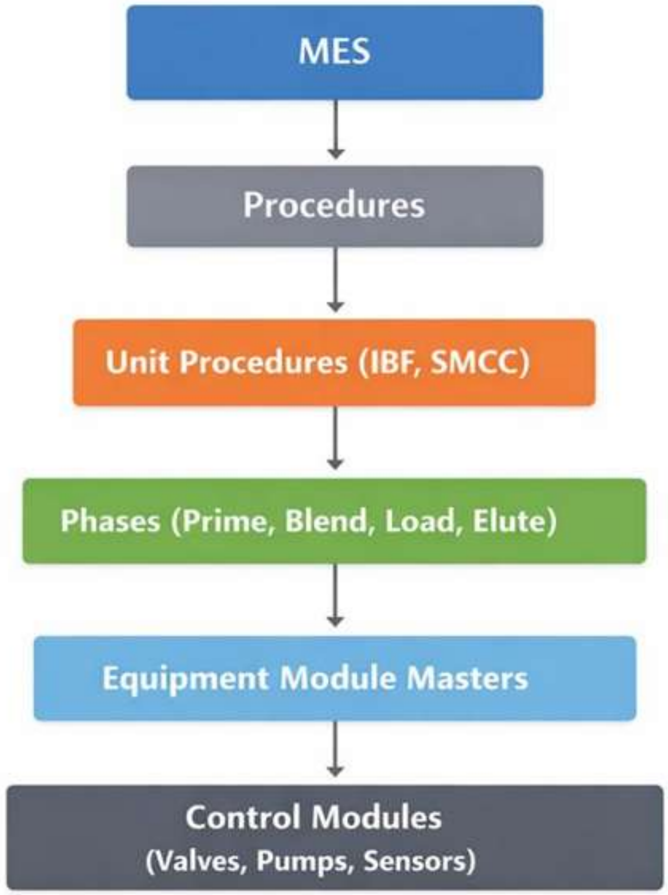

Figure 1:H-ISA88-DAF Hierarchical Architecture for IBF and SMCC Systems

This hierarchical structure implements six distinct control tiers, each with clearly defined responsibilities, interface specifications, and information exchange protocols. At the apex, the **Manufacturing Execution System (MES)** layer provides enterprise-level capabilities including recipe management with version control and electronic approval workflows, material tracking through unique lot identifiers and genealogy relationships, batch record generation with 2,500-4,000 data points per batch, regulatory compliance documentation supporting FDA inspection requirements and 21 CFR Part 11 audit trails, and production scheduling optimizing equipment utilization across 10-50 parallel manufacturing operations. The MES layer downloads complete recipe definitions containing 150-300 individual parameters to procedural control layers with transfer times of 2-8 seconds and cryptographic verification ensuring data integrity, while receiving real-time process data sampled at 0.5-5 Hz intervals, alarm notifications with <2 second latency from detection to MES update, and batch completion status with material yields and quality attribute summaries.

The **Procedure** layer represents the highest level of automated process control, coordinating complete manufacturing operations that may span multiple process units, extend across 8-72 hour durations, and involve 5-15 distinct unit operations. For downstream processing operations, a typical procedure orchestrates buffer preparation through IBF units (15-45 minute formulation campaigns), sequential chromatography steps through SMCC units (4-12 hour cycles per column), material transfers between

10.48047/jocaaa.2026.35.03.06

unit operations with volume verification (±2% accuracy), and handoffs to downstream operations such as ultrafiltration (2-6 hour concentration operations) or formulation systems (1-4 hour blending operations). Procedures implement high-level sequencing logic managing unit procedure initiation based on upstream completion and resource availability, exception handling for unit-level failures with automatic safe-state transitions, and material balance verification comparing input quantities to output yields with acceptable losses of 2-8% depending on unit operation.

Unit Procedures decompose complete procedures into unit-specific operation sequences with defined start and end points, material inputs and outputs, and quality verification criteria. The IBF Unit Procedure manages the complete buffer formulation and delivery cycle for a specific buffer type (e.g., Equilibration Buffer: 20 mM Sodium Phosphate pH 7.2, 150 mM NaCl, conductivity 15.5 mS/cm), encompassing skid priming (5-15 minutes), formulation with real-time quality monitoring (continuous operation at 50-500 L/h), quality verification confirming specifications before delivery authorization (pH ±0.05 units, conductivity ±2% of target), and delivery to consumers with flow rate coordination (matching consumer demand ±5%). The SMCC Unit Procedure coordinates a complete chromatography separation including column preparation through equilibration (3-5 column volumes over 15-45 minutes), product loading with optional breakthrough monitoring (100-500 L processed over 2-8 hours), washing to remove unbound material (3-7 column volumes over 20-60 minutes), elution for product recovery (gradient or step elution over 30-90 minutes collecting 2-8 column volumes), and regeneration preparing resin for subsequent cycles (cleaning and sanitization over 1-3 hours). Each Unit Procedure operates semi-independently with internal state management, resource reservation, and quality monitoring, while coordinating with other Unit Procedures through defined handshaking protocols for material transfer (upstream provides material availability signal, downstream confirms receipt capacity and authorization), resource sharing (IBF provides buffer availability, SMCC reserves required volumes), and exception propagation (upstream failures trigger downstream holds, quality failures prevent material advancement).

The **Phase** layer implements the most granular procedural control elements, representing executable control sequences with defined entry conditions, control logic, and completion criteria that typically execute over 2-120 minute durations depending on phase type and process scale. Common phases across IBF and SMCC operations include:

- **Prime Phase**: Systematically removes air from process lines, prepares inlet manifolds and pump suction lines, and establishes verified flow conditions through timed pump operations (30-180 seconds per inlet), air detection interlocks monitoring for bubble passage and triggering repriming, volumetric verification confirming 95-105% of expected displacement, and drain operations flushing 1.5-3x line volumes to waste. Prime phases execute 3-12 individual inlet preparations per skid with a total duration of 5-20 minutes, depending on system complexity and inlet count.
- **Blend Phase**: Executes real-time formulation control maintaining pH (±0.02-0.05 pH units from setpoint), conductivity (±1-3% of target), temperature (±0.5-1°C), and flow specifications (±2-5% of setpoint) through coordinated pump modulation with 0.5-2 second control loop update intervals, continuous analytical feedback from inline sensors (pH response time <30 seconds, conductivity response time <15 seconds, temperature response time <45 seconds), automated valve positioning for stream selection (actuation time 2-5 seconds), and proportional-integral control algorithms with tuning parameters optimized for system hydraulics (K_p = 0.5-2.0, K_i = 0.1-0.5 depending on loop). Blend phases continue indefinitely,y maintaining specifications until

10.48047/jocaaa.2026.35.03.06

external termination commands from consumer units or quality excursion detection triggering automatic drain diversion within 3-8 seconds.

- **Load Phase**: Manages product or buffer loading to chromatography columns implementing flow control maintaining target linear velocity (100-300 cm/h) through pump modulation with ±3-5% stability, volume totalization tracking cumulative delivery with ±1-2% accuracy, optional breakthrough monitoring measuring UV absorbance at column outlet with 0.001-0.01 AU resolution triggering column switching when threshold exceeded (typically 5-10% of loading plateau absorbance), and pressure monitoring detecting fouling (gradual pressure rise >20% indicating resin compression or particulate blockage) or channeling (sudden pressure drop >15% indicating flow bypass). Load phases execute for 1-8 hours, processing 100-2000 L depending on column size (typically 20-200 L resin volume) and loading density (20-50 g product/L resin for Protein A, 50-150 g product/L resin for ion exchange).
- **Elute Phase**: Controls gradient formation for product recovery through precise pump flow ratio control (±2% accuracy for binary gradients, ±3% for ternary gradients), monitors UV absorbance at dual wavelengths (280 nm for protein detection with 0.001-0.01 AU resolution, 260 nm for nucleic acid monitoring) for product detection and collection triggering, coordinates collection vessel switching based on optical density thresholds (collection start typically 0.05-0.1 AU ascending threshold, collection stop 0.02-0.05 AU descending threshold) with valve actuation latency <5 seconds minimizing product loss, and executes post-elution line recovery operations flushing 0.5-2 column volumes recovering 95-98% of holdup volume product. Elution phases recover product in 2-8 column volumes over 30-120 minutes with typical yields of 90-98% of loaded material.

Equipment Module Masters provide supervisory control, coordinating multiple Equipment Modules (typically 3-8 per unit) and Control Modules (typically 15-40 per unit) to execute phase commands while managing equipment-level state machines, exception conditions, and operational mode transitions. The Equipment Module Master implements state machine logic defining 8-15 permissible operational states including Hold (equipment idle, awaiting phase commands, all automated valves in safe positions), Monitor (continuous parameter surveillance without active control, data logging at 0.5-2 Hz), Prime (systematic air removal executing timed sequences with verification), Equilibrate (column conditioning establishing baseline conductivity and pH within ±5% of buffer values), Load (product or buffer delivery with volume tracking and optional breakthrough detection), Wash (unbound material removal requiring 3-7 column volumes), Elute (product recovery with gradient control and UV monitoring), Regenerate (resin cleaning with caustic or acid solutions at elevated temperatures 40-80°C for 30-120 minutes), and CIP (Clean-In-Place executing validated cleaning cycles with time, temperature, conductivity, and flow verification). State transitions follow recipe-defined sequences with 25-60 defined transition pathways per Equipment Module Master, incorporating prerequisite checks (required resources available, previous state completed successfully, quality parameters within specifications), concurrent operations management (multiple columns in different states sharing resources), and exception handling pathways. Exception conditions including sensor failures (out-of-range readings, communication timeouts >5 seconds, calibration expiration), limit violations (pressure exceeding 5-10 bar limits, temperature exceeding setpoint ±5°C, flow deviating >15% from target), equipment malfunctions (pump failures, valve position disagreements, leak detection), and communication timeouts (MES connection loss >30 seconds, field device communication failure >10 seconds) trigger safe shutdown pathways preventing equipment damage (pressure relief, pump stops, valve safe positions), product loss (collection to dedicated recovery

10.48047/jocaaa.2026.35.03.06

vessels, hold states maintaining product integrity), or cross-contamination (automated flushing sequences, drain diversions).

Equipment Modules encapsulate functionally related control components, providing standardized interfaces to Equipment Module Masters while managing internal control complexity, coordinating 2-8 subordinate Control Modules, and implementing equipment-specific control strategies. Representative Equipment Modules include:

- **Buffer Pump Control Module**: Manages 2-6 individual pumps (peristaltic pumps with 0.1-50 L/h capacity, diaphragm pumps with 1-200 L/h capacity) with variable flow rate control through 0-100% output commands or direct flow setpoints, coordinates pump sequencing to prevent supply interruption during pump changeovers (lead-lag configuration with automatic switchover when lead pump reaches capacity limit or failure detection), implements flow totalizers tracking cumulative delivery with ±1-2% accuracy over 10-10,000 L ranges enabling volumetric advancement criteria, provides pump health monitoring tracking operating hours (alerting at 80% of manufacturer-recommended replacement interval), detecting abnormal vibration or temperature (sensors with ±0.5°C accuracy), and managing preventive maintenance schedules. Pump Control Modules interface with 3-6 subordinate Control Modules (individual pump controllers, flow meters, pressure sensors), coordinating their operation to meet Equipment Module Master flow demands while maintaining pressure limits (typically 2-8 bar maximum to prevent tubing rupture or valve damage).
- **Valve Manifold Module**: Controls 8-30 automated valves organized by function including WFI supply manifold (3-8 valves providing Water for Injection to various inlets with individual isolation capability), buffer concentrate delivery manifold (4-12 valves selecting specific concentrate sources with interlock logic preventing simultaneous incompatible valve openings such as acid and base concentrates), product routing manifold (3-8 valves directing flow to process, collection, or drain with position verification within 1-3 seconds), and drain selection manifold (2-5 valves choosing appropriate waste destinations based on content classification). Implements comprehensive valve interlock logic preventing incompatible simultaneous valve states through boolean logic matrices (150-400 interlock rules per manifold depending on complexity), provides valve position feedback through limit switches (confirming open/closed states within 0.5-2 seconds of command) or smart positioners (providing continuous position indication for modulating valves with ±1-2% accuracy), manages valve cycling counters alerting when approaching manufacturer-specified lifetime limits (typically 100,000-1,000,000 cycles depending on valve type), and coordinates valve sequencing during transitions preventing transient pressure spikes (sequential opening with 0.5-2 second delays) or flow interruptions (make-before-break switching for critical paths).
- **Analytical Instrument Module**: Coordinates pH sensors (glass electrode or solid-state with ±0.02-0.05 pH unit accuracy over pH 2-12 range, response time <30 seconds to 90% of step change), conductivity transmitters (contacting or toroidal with ±1-2% accuracy over 0.1-200 mS/cm range, temperature compensation with ±0.5°C accuracy, response time <15 seconds), UV absorbance detectors (dual wavelength 260/280 nm with 0.001-0.01 AU resolution, 2-10 mm pathlength flow cells with 10-100 µL internal volume, response time <5 seconds), and temperature sensors (RTD or thermocouple with ±0.1-0.5°C accuracy over 0-100°C range). Implements sensor selection logic when multiple sensors exist per measurement type (automatic switching to backup sensor upon primary failure detection within 5-10 seconds, cross-validation

10.48047/jocaaa.2026.35.03.06

between redundant sensors alerting when disagreement exceeds ±5% of reading), provides temperature compensation for pH and conductivity measurements using established coefficients (pH: -0.003 to +0.003 pH units/°C depending on buffer composition, conductivity: +1.8 to +2.2%/°C), manages alarm limits with multiple severity levels (warning thresholds at ±10% of specification triggering operator notification, critical thresholds at ±20% triggering automatic diversion or hold states), calibration status tracking alerting when approaching expiration (typically 7-30 day intervals for pH, 30-90 days for conductivity, 90-180 days for UV depending on application criticality), and sensor health diagnostics including impedance monitoring for pH electrodes (alerting when exceeds manufacturer specifications indicating fouling or aging), cell constant verification for conductivity (comparing standard solution measurements to expected values within ±3%), and lamp intensity monitoring for UV detectors (alerting at <50% of initial intensity indicating lamp aging requiring replacement).

At the foundation, **Control Modules** represent individual field devices executing basic control functions under Equipment Module supervision, implementing single-loop control strategies, providing direct device interfaces, and maintaining minimal internal logic for safe operation. Control Modules encompass:

- **Automated Valve Control Modules**: Interface pneumatic solenoid valves (2-position on/off with 2-5 second actuation time, fail-safe spring return to defined position upon air pressure loss), motorized ball valves (0-90° rotation in 5-15 seconds with intermediate positioning capability for modulating service), and diaphragm valves (sanitary design with 3-8 second actuation, suitable for high-purity applications). Implement position feedback monitoring through limit switches (confirming commanded position reached within expected timeframe ±20%), execute safety interlocks at device level (preventing opening when upstream/downstream pressure differential exceeds design limits typically 5-10 bar), report valve status including position (open/closed/intermediate for modulating valves), fault conditions (failure to reach commanded position within timeout period, position disagreement between command and feedback lasting >3 seconds), and cycle count to parent Equipment Modules.
- **Pump Control Modules**: Manage variable frequency drives for centrifugal pumps (0-3600 RPM with ±0.1% speed accuracy), peristaltic pump controllers (0-600 RPM with tube life tracking based on manufacturer curves indicating replacement at 80-95% of rated life typically 100-500 operating hours), and diaphragm pump actuators (pneumatic or hydraulic with stroke frequency 20-200 cycles/minute). Provide motor protection through current monitoring (alerting when exceeds 110% of rated current indicating overload, tripping at 130% preventing motor damage), vibration monitoring for rotating equipment (accelerometers with 0.1-100 Hz frequency range alerting when vibration exceeds baseline by >50%), temperature monitoring (motor windings and bearing temperatures with ±1°C accuracy alerting at manufacturer-specified limits typically 80-120°C), and automatic shutdown upon fault detection within 0.1-1 second preventing equipment damage.
- **Sensor Control Modules**: Condition analog signals from field instruments (4-20 mA current loops with ±0.1% linearity, 0-10 VDC voltage signals with ±0.5% accuracy) converting to engineering units through calibrated scaling factors (slope and offset determined during commissioning with verification every 6-12 months), implement signal filtering (low-pass filters with 0.1-5 Hz cutoff frequency removing high-frequency noise while preserving process dynamics), provide sensor excitation power (24 VDC at 50-500 mA for powered transmitters with regulated supplies maintaining ±2% voltage stability), detect sensor faults through range

10.48047/jocaaa.2026.35.03.06

checking (values outside 0-105% of calibrated span indicating wiring faults or sensor failures), rate-of-change limiting (rejecting readings changing faster than physically possible rates indicating transient electrical interference), and communication timeout detection (alerting when no signal update received within expected interval typically 1-10 seconds depending on device). Report measured values to parent Equipment Modules at configured sample rates (typically 0.5-5 Hz for process control, 0.1-1 Hz for trending and batch records), quality status indicators (good/uncertain/bad based on sensor diagnostics), and alarm conditions (high/low limits, rate-of-change, sensor failure).

This hierarchical decomposition provides multiple architectural benefits essential for pharmaceutical automation, addressing regulatory, operational, and economic requirements. **Validation efforts scope naturally** to defined boundaries with clear deliverable sets: Control Modules undergo Factory Acceptance Testing (FAT) executing 15-30 test cases per module verifying basic functionality, response to commands, and fault detection with typical effort 4-12 person-hours per module; Equipment Modules receive Site Acceptance Testing (SAT) confirming proper integration through 30-60 test cases per Equipment Module including interface verification with subordinate Control Modules and parent Equipment Module Masters, alarm response validation covering all defined alarm conditions, and failure mode testing simulating sensor failures and equipment malfunctions with typical effort 20-60 person-hours per Equipment Module; Phases undergo Installation Qualification (IQ) verifying physical installation through 40-80 inspection points per phase, Operational Qualification (OQ) confirming functional operation through 50-120 test cases including normal operation across setpoint ranges, boundary conditions testing at specification limits, and exception handling validation with typical effort 60-150 person-hours per phase; complete Procedures face Performance Qualification (PQ) demonstrating proper function through 3-5 consecutive successful executions at nominal operating conditions and 2-3 executions at extreme operating points (minimum/maximum flow rates, shortest/longest phase durations, multiple concurrent operations) with total validation effort typically 300-800 person-hours per automated unit.

Change control impacts remain contained through modular boundaries enabling graduated revalidation approaches: modifications to Control Module logic (updating PID tuning parameters, adjusting alarm limits within validated ranges, correcting minor logic errors) require revalidation only of affected Equipment Modules and dependent phases with typical revalidation effort 15-40 person-hours and 1-2 week duration; Equipment Module changes (adding pumps to existing manifold, upgrading sensor types, modifying coordination logic) necessitate phase-level revalidation but not necessarily procedure-level retesting with typical effort 40-120 person-hours and 2-4 week duration; Phase modifications (adjusting advancement criteria, adding optional steps, changing setpoint ranges) require Unit Procedure validation but not full Procedure revalidation with typical effort 80-200 person-hours and 3-6 week duration. This graduated approach reduces validation burden by 40-55% compared to monolithic architectures requiring complete revalidation for any modification, while maintaining system integrity and regulatory compliance. Industry data indicates that facilities with well-implemented modular architectures execute 8-15 system improvements annually (versus 2-5 for monolithic systems) while maintaining equivalent or superior compliance metrics (deviation rates, regulatory inspection findings, batch record review efficiency), enabling continuous process improvement without prohibitive validation overhead that would otherwise constrain innovation and process optimization initiatives.

Troubleshooting follows structured pathways aligned with hierarchical boundaries facilitating rapid fault isolation and resolution: Control Module faults manifest as specific device malfunctions (valve

10.48047/jocaaa.2026.35.03.06

failing to open, sensor reading out of range, pump not responding to speed commands) indicating wiring problems, device failures, or calibration drift with troubleshooting focused on specific device location and type, typically requiring 15-45 minutes investigation and 30-120 minutes repair; Equipment Module failures suggest coordination logic errors (pumps not sequencing properly, valves opening in wrong order, sensors not switching correctly) indicating software configuration problems or Equipment Module Master communication issues, typically requiring 30-90 minutes investigation and 1-4 hours resolution through software adjustments; Phase execution problems point to procedural logic issues (incorrect advancement criteria, inappropriate setpoints, missing interlocks) or recipe parameter errors, typically requiring 1-3 hours investigation reviewing batch records and 2-8 hours resolution through procedural logic or recipe corrections. Mean time to repair (MTTR) for facilities implementing comprehensive H-ISA88-DAF architectures averages 2.5-4.5 hours across all fault types compared to 4.5-8 hours for less structured automation approaches, representing 40-50% improvement in maintenance efficiency and corresponding reductions in unplanned downtime.

System expansion accommodates gracefully through standardized interfaces and modular addition: new Control Modules integrate into existing Equipment Modules by adding device configurations (I/O channel assignments, scaling parameters, alarm limits) without modifying existing Control Module logic, typically requiring 4-12 hours engineering effort, 2-4 hours commissioning, and 8-20 hours validation per added device; new Equipment Modules incorporate into Equipment Module Masters through defined interface templates (standard command structures, status reporting formats, alarm propagation protocols) enabling rapid integration typically requiring 20-60 hours engineering, 1-2 days commissioning, and 40-80 hours validation per Equipment Module; new Phases add to Unit Procedure libraries through copy-modify-test workflows leveraging existing phase templates typically requiring 40-120 hours engineering, 2-5 days commissioning, and 80-200 hours validation per new phase. Facilities report 30-50% reduction in automation engineering effort for capacity expansions (adding parallel process trains), 35-55% reduction for product introductions (new recipes leveraging existing phase libraries), and 40-60% reduction for process improvements (modifying existing procedures) compared to projects requiring custom automation development without leveraging standardized frameworks.

The Physical Model decomposition for both IBF and SMCC units follows these established hierarchical principles, enabling modular design, systematic validation, and operational flexibility. Equipment Modules encapsulate related control functionality including pump control modules managing 2-6 pumps with variable flow rates spanning 0.1-200 L/h ranges, valve manifold modules controlling 8-30 automated valves with 2-5 second actuation times, and analytical instrument modules incorporating pH sensors (±0.02-0.05 pH units accuracy), conductivity transmitters (±1-2% accuracy over 0.1-200 mS/cm), and UV absorbance detectors (0.001-0.01 AU resolution) with appropriate temperature compensation. Control Modules represent individual field devices executing basic control functions under Equipment Module supervision including automated valve actuators (pneumatic solenoid valves with 2-5 second actuation, motorized ball valves with 5-15 second rotation, sanitary diaphragm valves with 3-8 second actuation), pump motor controllers (variable frequency drives with ±0.1% speed accuracy, peristaltic controllers with tube life tracking), and sensor signal conditioners (4-20 mA loops with ±0.1% linearity, 0-10 VDC with ±0.5% accuracy). This hierarchical organization facilitates validation with clearly scoped deliverables, maintenance with structured troubleshooting pathways, and future expansion through standardized integration interfaces while maintaining clear boundaries between automation components, preventing propagation of modifications across validation boundaries.

10.48047/jocaaa.2026.35.03.06

The Procedural Model implementation introduces phases designed to manage complex process transitions, quality monitoring, and resource coordination specific to biopharmaceutical manufacturing requirements,s addressing both operational and regulatory needs. Phases incorporate real-time analytical feedback enabling dynamic process adjustments based on pH measurements (±0.02-0.05 pH unit accuracy with <30 second response time), conductivity measurements (±1-2% accuracy with <15 second response), flow measurements (±2-5% accuracy with <5 second response), and ultraviolet absorbance measurements (0.001-0.01 AU resolution with <5 second response) captured at appropriate sampling intervals (0.5-5 Hz depending on criticality). Research exploring design patterns for pharmaceutical automation has demonstrated that well-structured phase logic incorporating quality monitoring and exception handling significantly reduces deviation rates while improving process robustness and product quality consistency. Implementation studies have shown that automation systems employing systematic design patterns for equipment module coordination and procedural control achieve 35-50% superior validation outcomes with 25-40% reduced commissioning time (12-20 weeks versus 18-30 weeks for less structured approaches), 30-45% lower post-validation modification rates (0.3-0.6 changes per year versus 0.8-1.5 changes per year), and 40-55% fewer validation deviations during qualification activities (2-5 deviations per unit versus 5-12 deviations per unit) [4]. This integration of continuous quality monitoring within discrete procedural elements represents a key innovation,n bridging batch control paradigms with process analytical technology requirements essential for modern bioprocessing,g enabling quality-by-design approaches where product quality attributes are built into processes through design rather than tested into products through final release testing.

Equipment Module Master logic provides supervisory control across multiple process states (typically 8-15 states per Equipment Module Master), coordinating lower-level equipment modules (3-8 Equipment Modules per Equipment Module Master) and control modules (15-40 Control Modules per Equipment Module Master) while managing exception conditions that may arise during processing. State machines define permissible transitions (25-60 transition pathways per state machine) and operational modes including Hold (idle awaiting commands), Monitor (continuous surveillance), Prime (preparation sequences), Equilibrate (column conditioning), Load (material delivery), Wash (cleanup operations), Elute (product recovery), Regenerate (resin cleaning), and CIP (equipment cleaning), ensuring process consistency and enabling systematic troubleshooting when deviations occur. The supervisory architecture facilitates integration with Manufacturing Execution Systems through standardized interfaces (OPC-UA, S88/S95 protocols with 2-8 second latency for command/response cycles), creating a cohesive framework from enterprise-level recipe management containing 150-300 parameters per recipe through field-level device control operating at 10-100 millisecond control loop update intervals. This multi-tiered architecture enables clear separation of concerns with Equipment Module Masters managing equipment-specific logic (state machines, resource coordination, local interlocks) while higher-level procedural control (Unit Procedures, Procedures) coordinates multiple equipment assemblies to execute complete manufacturing operations spanning 4-72 hours and involving 5-15 unit operations. The resulting system provides operators with consistent interfaces minimizing training requirements (operators proficient on one unit readily transfer skills to other units using common architecture), simplified troubleshooting workflows with hierarchical fault isolation reducing mean time to repair by 40-50%, and flexibility necessary to accommodate process improvements (25-40% faster implementation cycles) and equipment modifications (30-45% reduced revalidation effort) throughout the facility lifecycle spanning 15-25 years from initial commissioning through eventual decommissioning.

10.48047/jocaaa.2026.35.03.06

Parameter	Continuous Downstream Processing	Pharmaceutical Automation Design Patterns
Operational Mode	Semi-continuous with process intensification	Modular coordination with systematic patterns
Control Philosophy	Individual cycles as discrete batch events	Structured phase logic with quality monitoring
System Architecture	Multi-column chromatography configurations	Equipment module coordination frameworks
Process Adaptation	ISA-88 principles applied to continuous systems	Exception handling integration
Implementation Outcome	Standardized automation across hybrid environments	Superior validation outcomes
Commissioning Impact	Preserved procedural logic with continuous flow	Reduced commissioning time requirements

Table 2: Continuous Processing and Automation Design Patterns for Biopharmaceutical Manufacturing [3,4]

3. Inline Buffer Formulation Automation Architecture

The Inline Buffer Formulation system represents a sophisticated automation challenge requiring precise simultaneous control of multiple independent variables including pH (±0.02-0.05 pH units from setpoint over pH 4-10 range), conductivity (±1-3% of target over 1-150 mS/cm range), temperature (±0.5-1°C over 15-35°C range), and flow rate (±2-5% of setpoint over 10-500 L/h range) while maintaining formulation accuracy and preventing out-of-specification material from reaching downstream processes. The system architecture accommodates dynamic addition or removal of 3-8 buffer concentrate streams with individual pumps modulating output at 0-100% capacity to achieve target specifications according to recipe parameters containing 150-250 individual setpoints, control parameters, and alarm limits downloaded from Manufacturing Execution Systems with 2-5 second transfer latency and cryptographic verification. This approach eliminates the delays (8-24 hours for batch preparation, quality testing, and approval) and quality risks (manual measurement and addition errors contributing to 15-25% of buffer preparation deviations in traditional batch methods) associated with traditional batch buffer preparation methods where buffers are mixed in 50-2000 L tanks, tested offline through manual sampling and laboratory analysis requiring 2-6 hours, and held pending quality approval before use consuming valuable facility space and inventory capital.

Contemporary research examining digital transformation in pharmaceutical manufacturing has highlighted the critical importance of inline processing technologies for improving manufacturing efficiency and reducing resource consumption while maintaining or enhancing product quality. Comprehensive investigations into digitalization strategies for biopharmaceutical production have demonstrated that inline buffer formulation systems provide substantial advantages over batch preparation methods, including 60-75% reduced preparation time (15-45 minutes for inline formulation versus 8-24 hours for batch preparation including mixing, testing, and approval), 40-60% decreased buffer inventory requirements (elimination of 200-2000 L hold tanks per buffer type, facilities typically maintaining 5-15 different buffer formulations), 30-45% improved formulation accuracy (inline real-time adjustment versus batch measurement and correction cycles), 70-85% reduction in buffer expiration losses (just-in-time production versus batch preparation with 7-30 day hold times before expiration), and 50-70% decrease in

10.48047/jocaaa.2026.35.03.06

facility footprint requirements for buffer preparation areas [5]. These systems enable just-in-time buffer delivery producing buffers on-demand at rates of 50-500 L/h that eliminates large-scale buffer storage requirements (8-16 m² floor space per 1000 L tank, 5-10 tanks typical per facility), reducing facility footprint by 40-80 m² while minimizing buffer expiration losses that occur with extended storage periods (2-8% of prepared buffer inventory expires before use in batch preparation facilities, representing $50,000-200,000 annual losses for typical biopharmaceutical facilities). Furthermore, inline formulation enables rapid buffer changeovers requiring 15-45 minutes for complete formulation transition (versus 4-12 hours for batch preparation of new formulation), supporting flexible manufacturing operations where multiple products or process variants may be executed within short timeframes (2-3 products per week versus 0.5-1 product per week with batch buffer preparation). Economic analyses indicate typical implementation costs of $800,000-1,500,000 per inline formulation system with payback periods of 24-42 months through operational savings (reduced buffer waste, decreased inventory, eliminated hold tank cleaning, lower quality control testing costs) and capacity improvements (reduced buffer preparation cycle times enabling increased facility throughput).

The Physical Model hierarchy positions IBF Skid as the Unit level containing 3-8 Equipment Modules and 15-40 Control Modules, with multiple Process Cells enabling parallel operation (typically 2-4 IBF skids per facility providing redundancy and capacity for concurrent operations) and dedicated suite allocation to prevent cross-contamination risks in multi-product facilities producing 3-8 different therapeutic products. Equipment Modules encapsulate functional subsystems with clearly defined interfaces and responsibilities, including the Buffer Pump Control Module managing 2-6 peristaltic pumps (0.1-20 L/h capacity, ±2% accuracy) or diaphragm pumps (5-200 L/h capacity, ±3% accuracy) with lead-lag coordination preventing supply interruption, the Water for Injection valve manifold module controlling 8-15 pneumatic automated valves (2-5 second actuation time) with interlock logic preventing incompatible simultaneous openings, the caustic valve manifold module for sanitization circuits controlling 3-6 automated valves enabling 0.5 M sodium hydroxide circulation at 60-80°C for 60-120 minutes, the salt valve manifold module for concentrate delivery managing 4-12 automated valves selecting sodium chloride solutions (1-5 M concentration), phosphate buffers (0.5-2 M concentration), and other concentrates, the shear blender control module with variable speed motors (1000-6000 RPM, ±1% speed accuracy) providing intensive mixing achieving <5% concentration variation across outlet flow stream within 2-5 second residence time, and the temperature control module with heat exchanger capability (5-50 kW heating/cooling capacity) maintaining setpoint ±0.5-1°C through modulating control valves and proportional-integral control (K_p = 1.5-3.0, K_i = 0.2-0.6). Control Modules represent individual field instruments with basic control functions, including automated control valves (pneumatic actuators with 3-8 second stroking time, fail-safe spring return to closed position), pH sensors (glass electrode or solid-state with ±0.02-0.05 pH unit accuracy over pH 2-12, 15-30 second response time to 90% of step change, calibration intervals 7-14 days using pH 4.00, 7.00, and 10.00 buffer standards), conductivity transmitters (contacting or toroidal with ±1-2% accuracy over 0.1-200 mS/cm, <15 second response time, automatic temperature compensation with ±0.5°C accuracy, calibration intervals 30-60 days using traceable conductivity standards), flow meters (magnetic flowmeters with ±0.5-2% accuracy over 1-500 L/h, 2-5 second response time, or Coriolis meters with ±0.1-0.5% accuracy providing density measurement enabling mass flow calculation), and pump motor controllers (variable frequency drives with 0-100% output commanding 0-3600 RPM with ±0.1% speed accuracy). This modular decomposition facilitates independent validation of subsystem components with clearly scoped test deliverables (15-30 test cases per Control Module during FAT, 30-60 test cases per Equipment Module during SAT),

10.48047/jocaaa.2026.35.03.06

maintenance through replacement of failed modules without affecting validated adjacent systems (mean time to repair 1.5-3.5 hours for Control Module replacement, 3-6 hours for Equipment Module repairs), and capacity expansion through addition of concentrate streams or increased pump capacity without complete system revalidation (graduated revalidation approach reducing effort by 40-55% compared to monolithic system modifications).

Phase design addresses the operational sequence required for reliable buffer formulation across diverse formulation requirements spanning pH 4-10, conductivity 1-150 mS/cm, and 15-30 different buffer compositions (phosphate, Tris, acetate, citrate bases with various salts and pH adjustment). The **Skid Prime** phase prepares inlet lines by priming selected pumps and inlets to drain, ensuring buffer concentrates reach appropriate positions without premature mixing that could cause precipitation (mixing concentrated phosphate with calcium-containing solutions), pH excursions (mixing concentrated acids with bases), or conductivity spikes (inadequate dilution of concentrated salt solutions). The phase sequences through 3-12 individual inlet preparations executing timed pump operations (30-120 seconds at 50-100% pump output), monitors for air detection through inline sensors (bubble detectors or conductivity drops indicating gas phase passage), performs volumetric verification confirming 95-105% of expected displacement based on pump calibration curves and line volumes (typically 0.1-2 L per inlet), and executes drain operations flushing 1.5-3x line volumes ensuring concentrate reaches distribution manifold without contaminating product paths. Industry literature examining inline dilution process monitoring has emphasized the importance of proper system preparation sequences to ensure formulation accuracy and prevent quality failures that could compromise downstream processing. Comprehensive studies have shown that systematic priming protocols incorporating volumetric verification and analytical monitoring during prime operations significantly reduce the risk of formulation errors during subsequent production phases, with facilities implementing validated prime sequences reporting 75-90% reduction in formulation deviation rates (from 8-15 deviations per 100 batches to 1-3 deviations per 100 batches) and 60-80% decrease in out-of-specification buffer incidents requiring investigation and corrective action [6]. Optional outlet flushing with Water for Injection (2-5 column volumes, typically 5-20 L depending on distribution line volume) prevents cross-contamination between different buffer formulations ensuring each new formulation begins with clean distribution lines free of residual previous buffers, critical when transitioning between products with different quality attribute specifications or switching between formulations with incompatible components (pH >2 unit difference, conductivity >50 mS/cm difference, or chemically incompatible solutes).

The **Inlet Prime** phase specifically addresses individual concentrate priming through tote tubing sets, with post-prime WFI flushing (0.5-1.5 L flush volumes) preventing adverse reactions between incompatible concentrates such as concentrated base solutions (1 M sodium hydroxide) and acidic phosphate buffers (1 M phosphoric acid) that could cause localized precipitation, temperature spikes (exothermic neutralization reactions releasing 20-60 kJ/mol), or pH excursions (>3 pH unit swings causing sensor range violations and control instabilities). This sequential approach, though requiring multiple phase executions (3-12 inlet primes) per complete system preparation consuming 15-30 minutes total duration, ensures system readiness and prevents quality excursions that could compromise downstream processing operations, cause product quality failures (protein precipitation, loss of biological activity, aggregation), or necessitate expensive column cleaning or resin replacement (column cleaning cycles consuming 6-12 hours and 50-200 L cleaning solutions, resin replacement costs $50,000-300,000 depending on resin type and column size).

10.48047/jocaaa.2026.35.03.06

The **Blend Phase** represents the core operational function implementing multiple control strategies simultaneously to achieve target buffer specifications with continuous quality monitoring and real-time adjustment capability. **Total Flow Control** maintains system throughput by modulating designated flow control pump(s) against flow setpoints spanning 50-500 L/h depending on downstream demand, implementing proportional-integral control (Kp = 0.8-2.0, Ki = 0.1-0.4) achieving ±2-5% flow stability under varying backpressure conditions (0.5-3 bar typical outlet pressures) and pump output limitations (maximum 100% output corresponding to pump maximum flow capacity). **Component Flow Control** ties individual concentrate pumps to dedicated flow meters, ensuring precise delivery rates for each concentrate stream, with flow ratios determined by recipe parameters (e.g., phosphate buffer diluted 1:20, salt solution diluted 1:50, caustic solution diluted 1:100) and adjusted in real-time based on analytical feedback. **Conductivity Control** utilizes either high-range conductivity meters (10-200 mS/cm with ±1% accuracy) or low-range meters (0.1-20 mS/cm with ±2% accuracy) depending on target formulation conductivity, adjusting pump output to maintain specification through proportional-integral control loops with tuning parameters (Kp = 1.0-2.5, Ki = 0.2-0.5) optimized for concentrate types (salt solutions providing rapid conductivity response within 5-15 seconds versus buffer concentrate additions showing delayed response over 15-45 seconds due to dilution and mixing dynamics). **pH Control** implements configurable direct-acting strategies (increasing acid pump output to decrease pH, typical for pH <7 buffers) or reverse-acting strategies (increasing base pump output to increase pH, typical for pH >7 buffers) with proportional-integral control parameters (Kp = 0.5-2.0, Ki = 0.05-0.3) accommodating both acidic control components (phosphoric acid, acetic acid, hydrochloric acid) and alkaline control components (sodium hydroxide, Tris base, ammonium hydroxide) to maintain pH within ±0.02-0.05 pH units around setpoints spanning typical buffer pH ranges (pH 4.5-8.5 for biopharmaceutical applications).

Additional control strategies address system-level requirements,s ensuring stable operation and quality assurance. **Forward Pressure Control** maintains utility supply pressure at 3-6 bar with ±0.2 bar stability using pneumatically-actuated control valves with 2-5 second response times on WFI supply headers, enabling concurrent operation of multiple IBF skids (2-4 skids typical per facility) without mutual interference through hydraulic coupling and ensuring adequate net positive suction head (NPSH) for downstream pumps preventing cavitation and flow instabilities. **Back Pressure Control** preconditions hydraulic conditions at system outlets maintaining 0.5-1.5 bar backpressure with ±0.1 bar stability through spring-loaded relief valves or pneumatically-controlled backpressure regulators, reducing transient flow disturbances during flowpath transitions from drain diversion to product delivery that otherwise cause temporary flow rate deviations of 10-25% lasting 5-20 seconds and corresponding pH and conductivity excursions requiring 30-90 seconds recovery time. **Shear Blender Mixing** operates dynamically with motor speed output scaled proportionally with total flow (typically 100-200 RPM per 100 L/h flow) to ensure adequate mixing intensity achieving Reynolds number >10,000 for turbulent mixing, producing <5% concentration variation across outlet flow stream measured at multiple radial positions, within short residence times (2-8 seconds) through the mixing head while preventing negative discharge pressure (<-0.2 bar) at pump outlets that would cause pump cavitation, air entrainment, or seal damage. **Temperature Control** maintains specification (typically 20-25°C ±1°C for ambient buffer formulation, 2-8°C ±0.5°C for cold buffer applications) and provides reference conditions for temperature-compensated pH measurements (calibrated at specific temperatures typically 25°C with automatic compensation using established coefficients -0.003 to +0.003 pH units/°C) and conductivity measurements (conductivity varies +1.8 to +2.2%/°C requiring automatic compensation to normalize readings to reference temperature 25°C enabling accurate comparison to specifications).

10.48047/jocaaa.2026.35.03.06

Integration with Manufacturing Execution Systems enables automated recipe execution triggered by downstream unit requests with minimal communication latency (2-8 seconds from request initiation through recipe download completion and phase execution authorization), implementing standardized communication protocols (OPC-UA, S88/S95 batch control standards) and secure data transfer with cryptographic verification (SHA-256 hashing), ensuring data integrity during transmission. The architecture supports multiple recipe types addressing different operational needs, including blend preparation recipes (15-30 minute duration) that ready the skid for buffer supply through prime sequences, quality verification, and hold state establishment, and complete blend recipes (continuous operation until external termination) that execute formulation and delivery sequences maintaining specifications while supplying 50-500 L/h to downstream consumers. This integration eliminates manual recipe loading that historically required 5-15 minutes operator interaction per recipe with 15-25% error rates based on comparative analysis of buffer preparation operations across multiple facilities, substantially reducing human error potential including incorrect setpoint entry (pH 7.2 entered as 7.8, conductivity 15.5 entered as 1.55), omitted parameters (missing alarm limits, undefined advancement criteria), and recipe version mismatches (using superseded recipe version instead of current validated version). Automated recipe management provides comprehensive batch records capturing 2,500-4,000 data points per batch (pH sampled at 1 Hz generating 3,600 values per hour, conductivity at 0.5 Hz generating 1,800 values per hour, flow at 2 Hz generating 7,200 values per hour, plus discrete events including valve state changes, pump output adjustments, alarm occurrences) for regulatory documentation supporting FDA inspections, annual product reviews, and continuous process verification programs while enabling sophisticated process monitoring through statistical process control (SPC) charts tracking process capability indices (Cpk values typically 1.5-2.5 for well-controlled formulation processes) and trending analysis identifying gradual process drift before specification violations occur.

Feature	Pharmaceutical Digitalization	Inline Dilution Process Monitoring
Technology Application	Inline processing for manufacturing efficiency	Real-time analytical monitoring during operations
Preparation Time	Just-in-time buffer delivery systems	Comprehensive priming protocols
Inventory Management	Eliminated large-scale buffer storage	Volumetric verification procedures
Formulation Accuracy	Improved precision over batch methods	Prevention of formulation errors
Facility Impact	Reduced footprint requirements	Quality assurance during prime operations
Operational Flexibility	Rapid buffer changeovers for multi-product facilities	Sequential system preparation sequences

Table 3: Digital Transformation and Inline Process Monitoring in Pharmaceutical Manufacturing [5,6]

4. Sequential Multi-Column Chromatography Automation Architecture

Sequential Multi-Column Chromatography represents an advanced purification strategy maximizing resin utilization and process efficiency through flexible, asynchronous scheduling of multiple chromatography columns operating in a coordinated fashion on offset timelines. The system accommodates three distinct operational modes addressing different process objectives and scale requirements: **Traditional**

10.48047/jocaaa.2026.35.03.06

Chromatography utilizing single columns for single separation steps achieving 50-65% dynamic binding capacity utilization at typical loading densities (20-35 g product/L resin for Protein A, 40-80 g product/L resin for ion exchange chromatography); **Sequential Chromatography with Breakthrough** employing 2-4 columns in series per step to achieve near-complete resin saturation, substantially exceeding dynamic binding capacity utilization reaching 85-95% through deliberate overloading of primary columns (loading densities 35-50 g/L for Protein A, 80-150 g/L for ion exchange) and capturing breakthrough product on secondary columns; and **Sequential Chromatography without Breakthrough** using single columns per step with sequential processing on 2-6 parallel columns maintaining continuous throughput with reduced bed heights (15-25 cm versus 25-40 cm for traditional columns) enabling faster cycle times (4-8 hours versus 8-16 hours traditional cycles) while maintaining acceptable resolution and yield (>95% product recovery, >98% impurity removal).

Contemporary research examining chromatography automation strategies has demonstrated the significant operational and economic benefits achievable through multi-column processing configurations addressing both resource utilization and process efficiency. Comprehensive studies investigating modular control systems for industrial liquid chromatography have shown that sophisticated automation architectures enable flexible column scheduling with asynchronous operation of 2-6 columns on offset timelines (typical offset 2-4 hours enabling continuous upstream processing), real-time process monitoring capturing pH (±0.02 pH units), conductivity (±1-2%), UV absorbance (0.001-0.01 AU resolution), and pressure (±0.5% over 0-10 bar range) at 1-5 Hz sampling rates, and adaptive control strategies optimizing separation performance through automated gradient optimization (adjusting gradient slope 0-100% buffer B over 5-20 column volumes based on real-time UV profile analysis), breakthrough detection (switching columns when UV absorbance exceeds 5-10% of loading plateau), and pressure-based fouling compensation (extending wash duration when pressure rises >20% above baseline) while minimizing resin consumption (40-60% reduction through breakthrough strategies) and buffer usage (30-45% reduction through optimized wash and equilibration volumes) [7]. These implementations incorporate advanced sensor technologies providing comprehensive process visibility (10-20 process variables monitored per column), predictive algorithms enabling feedforward control (adjusting downstream parameters based on upstream measurements reducing response lag by 60-80%), and equipment module coordination logic facilitating complex multi-column operations (managing 30-80 automated valves, 5-12 pumps, 8-16 analytical sensors per SMCC system) previously requiring extensive manual intervention (4-8 operator hours per cycle for manual multi-column operations versus 0.5-1.5 hours for automated systems). The resulting systems achieve superior resource utilization (resin costs $50,000-300,000 per column, 40-60% utilization improvement yielding $20,000-180,000 annual savings per column), enhanced productivity (30-50% throughput increase through continuous operation versus batch operation), and improved consistency (process coefficient of variation reduced from 12-18% to 4-8% through automated control) while maintaining or improving product quality through reproducible processing conditions (batch-to-batch yield variation <5%, purity variation <2%).

The Physical Model encompasses three primary equipment assemblies working in coordinated fashion with clearly defined interfaces and resource-sharing protocols. The **SMCC skid** provides essential utilities and control capabilities including pumping capabilities with 3-8 individual pumps spanning capacity ranges (0.1-5 L/min low flow pumps for analytical and equilibration steps, 5-50 L/min high flow pumps for loading and washing operations) and gradient formation through binary or ternary pump systems achieving ±2-3% composition accuracy; extensive valving with 30-80 automated pneumatic valves (2-5 second actuation time, fail-safe positions defined for each valve preventing cross-

10.48047/jocaaa.2026.35.03.06

contamination or product loss upon power failure) enabling complex flowpath configurations routing flows between 8-15 inlet sources (buffer bags, product sources, cleaning solutions), 2-6 chromatography columns, and 6-12 outlet destinations (collection vessels, drain, recirculation paths); filtration with 0.2-0.45 μm pore size filters (effective area 0.01-0.1 m² depending on flow rate requirements) removing particulates protecting columns from fouling; bubble separation with 0.5-2 L capacity degassing chambers or inline bubble traps preventing air entrainment during column operations that would cause flow distribution problems, resin bed lifting, and UV absorbance artifacts; and analytical instrumentation including dual-wavelength UV detectors (280 nm for protein monitoring with 0.001-0.01 AU resolution, 260 nm for nucleic acid detection, 2-10 mm pathlength flow cells with 10-100 μL internal volume minimizing dispersion), pH sensors (±0.02-0.05 pH units accuracy over pH 2-12 range with <30 second response time), and conductivity meters (±1-2% accuracy over 0.1-200 mS/cm range with <15 second response time and automatic temperature compensation) spanning necessary measurement ranges for diverse buffer compositions.

The **chromatography column** itself contains stationary phase resin with carefully controlled properties including particle sizes (typically 30-90 μm for preparative chromatography balancing resolution and pressure drop, 10-30 μm for analytical applications), pore sizes (30-400 nm depending on target molecule size, smaller pores for small molecules <10 kDa, larger pores for large proteins and virus particles >100 kDa), and ligand densities (20-50 μmol/mL for ion exchange resins, 10-30 mg protein A/mL resin for affinity chromatography) appropriate for target molecule separation mechanisms including charge-based separation (ion exchange), hydrophobicity (hydrophobic interaction, reversed phase), size (size exclusion), and biospecific recognition (affinity chromatography). Mobile phase fluids flow at controlled linear velocities (100-400 cm/h, depending on resin type and particle size, higher velocities enabled by smaller particles and rigid resin matrices) across resin beds to achieve separation based on differential retention of molecular species. Typical preparative column dimensions span wide ranges including diameters (5-80 cm for process development through commercial scale, cross-sectional areas 20-5000 cm²) and bed heights (10-40 cm balancing resolution requirements against pressure drop and buffer consumption), containing substantial resin volumes (1-100 L for commercial operations, larger columns up to 200 L for high-throughput facilities) with associated significant material costs ($50,000-300,000 per column fill depending on resin chemistry, Protein A resins costing $15,000-25,000/L, ion exchange resins $3,000-8,000/L, hydrophobic interaction resins $5,000-12,000/L).

The **Buffer Bag Station** stores formulated buffers in single-use bags (typically 50-500 L capacity polyethylene or fluoropolymer bags qualified for biopharmaceutical applications, USP Class VI materials) and initiates refill operations from IBF systems when weight measurements from load cells (±0.1-0.5 kg accuracy over 0-500 kg range) indicate capacity below threshold values (typically refill initiated at 20-30% remaining volume ensuring adequate supply during ongoing column operation). The station includes conductivity monitoring (±1-2% accuracy) for formulation verification comparing measured values against recipe specifications (accepting batches within ±5% of target conductivity), temperature monitoring (±0.5°C accuracy) ensuring buffers remain within specification (typically 20-25°C ±2°C preventing protein precipitation or microbial growth), and automated connections through single-use aseptic connectors (sterile connection established in <5 minutes without environmental exposure) enabling closed-system operation preventing contamination during buffer transfer operations.

The Equipment Module architecture reflects functional subsystems with clearly defined responsibilities and standardized interfaces enabling modular operation, maintenance, and validation. **Distribution Units** manage critical buffer station functions including bag weighing with load cells (±0.1-0.5 kg accuracy

10.48047/jocaaa.2026.35.03.06

enabling precise volume determination within ±1-2% through density calculations), conductivity monitoring (±1-2% accuracy with <15 second response time) verifying formulation specifications before authorizing use, flow control maintaining target delivery rates (50-500 L/h) with ±3-5% stability through pump modulation or pressure regulation, pumping with peristaltic pumps (0.5-20 L/h capacity for low flow applications) or diaphragm pumps (10-200 L/h capacity for high flow operations), pressure sensing across required ranges (0-5 bar typical with ±0.5% accuracy) detecting supply problems or line blockages, and WFI manifold operations controlling 6-12 automated pneumatic valves (2-5 second actuation) managing water for injection distribution to various cleaning and preparation functions.

SMCC Train Units incorporate comprehensive monitoring and control capabilities including bubble trap control with level switches (float switches or capacitance sensors with ±5 mm accuracy) and automatic vent valves (pneumatic normally-closed valves opening to atmosphere when bubble accumulation detected) maintaining acceptable gas volume limits (<5% column volume preventing flow distribution problems), differential pressure monitoring across columns (0-5 bar range with ±0.02-0.1 bar precision depending on column size) enabling detection of fouling (gradual pressure increase >20% over multiple cycles indicating accumulating particulates or resin compression) and channeling (sudden pressure drop >15% indicating preferential flow paths bypassing resin bed), column conductivity measurement with temperature compensation (±1-2% accuracy over 0.1-200 mS/cm) monitoring buffer transitions and gradient formation, flow control and totalization with ±2-5% accuracy and 0.01-1 L resolution enabling precise volume-based advancement criteria (load 150.0 ±7.5 L, wash 3.00 ±0.15 column volumes), pump control with variable frequency drives (0-100% output commanding 0-3600 RPM with ±0.1% speed accuracy) enabling modulated flow delivery, and UV sensor selection and control with automatic range switching capability (0.01-3 AU full scale ranges) accommodating varying absorbance levels during different process steps (loading typically 0.5-2 AU, elution peaks 2-5 AU, equilibration baseline <0.02 AU).

Buffer Bag Units provide weighing with ±0.1-0.5 kg accuracy enabling precise volume determination (calculating volume from weight using density 0.99-1.05 g/mL depending on buffer composition with ±1-2% accuracy), conductivity monitoring (±1-2% accuracy with <15 second response) for formulation verification before use, temperature monitoring (±0.5°C accuracy) ensuring specifications maintained during storage (preventing precipitation, microbial growth, or chemical degradation during hold periods typically <7 days), and level monitoring through weight trending (detecting consumption rate 10-500 L/h and projecting depletion time) triggering automated refill requests when capacity falls below threshold (typically 20-30% remaining volume providing 30-90 minute reserve before depletion). This modular decomposition facilitates independent operation of buffer supply, column processing, and analytical monitoring, maintenance through module replacement without affecting adjacent systems (mean time to repair 2-5 hours for module-level repairs versus 6-15 hours for monolithic systems), and validation with clearly scoped deliverables (30-60 test cases per Equipment Module during SAT) with documented improvements in mean time to repair (40-50% reduction compared to monolithic architectures) and mean time between failures (25-35% improvement through isolated fault containment).

Calculated variables provide critical process metrics essential for chromatography operations, enabling real-time process monitoring, quality verification, and automated decision-making. **Height Equivalent to a Theoretical Plate (HETP)** calculations quantify column efficiency through residence time distribution analysis of tracer substances (typically acetone, sodium chloride solutions, or uracil for different mobile phase compositions) injected as narrow pulses (0.1-0.5% column volume) and detected through UV absorbance or conductivity measurements. HETP values calculated from retention time (first moment of

10.48047/jocaaa.2026.35.03.06

peak), peak width at half-height (measuring band spreading), and peak asymmetry factors (comparing leading to trailing edge slopes) indicate proper packing quality, with acceptable HETP values typically 0.3-0.8 mm (1-3 times particle diameter) and asymmetry factors 0.8-1.5 (values <0.8 indicating leading peaks from channeling, values >1.5 indicating tailing from dead volumes or poor packing). **Column differential pressure monitoring** enables detection of fouling (gradual pressure increase >20% over 5-20 cycles indicating accumulating particulates, resin compression, or chemical fouling), channeling (sudden pressure decrease >15% indicating preferential flow paths bypassing resin bed causing reduced separation efficiency), or other column integrity issues (seal failures, resin bed settling creating voids at top of bed). **Gradient flow calculations** determine proportional flow rates for binary gradients (two pumps mixing buffer A and buffer B at variable ratios achieving 0-100% buffer B composition with ±2-3% accuracy) or multi-component mobile phase gradients (ternary or quaternary systems using 3-4 pumps) with mathematical precision through real-time flow ratio adjustments based on gradient table specifications (defining %B versus column volume or time), enabling reproducible gradient profiles (batch-to-batch variation <2% in gradient composition at equivalent column volumes). **Column volume calculations** determined from measured diameter (±0.1-0.5 cm accuracy using calipers or automated measurement) and bed height (±0.1-0.5 cm accuracy from column ruler or automated level detection) establish the reference scale for buffer consumption (3-12 column volumes per cycle typical) and product elution criteria (collection window typically 1.5-4 column volumes centered on elution peak) with acceptable uncertainty levels (±2-5% in calculated column volume propagating from diameter and height measurement uncertainties).

Research examining continuous downstream processing technologies has emphasized the importance of sophisticated control strategies for multi-column operation,s addressing both operational complexity and economic optimization. Comprehensive investigations into integrated continuous biomanufacturing have demonstrated that breakthrough strategies deliberately overloading primary columns to 110-130% of dynamic binding capacity and capturing breakthrough product on secondary columns connected in series achieve substantial improvements in resin utilization (85-95% capacity utilization versus 50-65% for traditional single-column approaches representing 40-60% improvement), though requiring precise volume-based switching (±2-5% accuracy in switched volume) between columns at predetermined loading volumes (calculated from historical breakthrough curves and updated based on real-time UV monitoring) and coordinated wash sequences recovering high product percentages (95-98% recovery from interstitial volumes) [8]. These studies have shown that automated control systems capable of managing complex column interconnections (30-80 automated valves coordinating 2-6 columns in various series, parallel, and independent configurations), synchronized but offset processing steps (typical 2-4 hour offsets between columns enabling continuous upstream processing without accumulation tanks), and real-time quality monitoring (UV absorbance at 0.001-0.01 AU resolution enabling breakthrough detection and product tracking) enable reliable multi-column operations with superior economic performance (30-40% reduction in cost of goods through improved yields and reduced resin/buffer consumption) compared to traditional single-column batch chromatography. Economic analyses indicate breakthrough strategies provide $150,000-500,000 annual savings per purification train through reduced resin consumption (40-60% utilization improvement on resin costing $50,000-300,000 per column), decreased buffer usage (25-35% reduction through optimized loading and washing), and improved product yields (2-5% yield improvement worth $50,000-200,000 annually depending on product value $5,000-50,000/g).

10.48047/jocaaa.2026.35.03.06

Control strategies address the sophisticated operational requirements of sequential multi-column processing, managing asynchronous column operation, resource coordination, and quality monitoring. The **Breakthrough strategy** optimizes resin utilization by deliberately overloading primary columns beyond traditional loading levels (110-130% of dynamic binding capacity versus 80-90% traditional loading) and capturing breakthrough product on secondary columns positioned in series, requiring precise volume-based switching accurate to ±2-5% tolerances (typical primary column loading 120-180 L, secondary column switching at 115-175 L based on historical breakthrough curves and real-time UV monitoring) between columns and coordinated wash sequences recovering 95-98% of product from interstitial volumes (2-5 column volumes wash applied to secondary column after disconnection from primary, product recovered in 1.5-3 column volumes). **Non-breakthrough sequential strategies** maintain traditional column loading levels (80-90% of dynamic binding capacity preventing breakthrough) while orchestrating 2-6 columns through synchronized but offset process steps with typical phase offsets of 2-4 hours (Column 1 in elution while Column 2 in equilibration and Column 3 in loading), ensuring at least one column remains in product-loading mode continuously to maintain upstream processing without accumulation tanks (eliminating 500-2000 L hold tanks with associated cleaning, quality testing, and hold time requirements).

Column Train Product Load Flow Control maintains consistent feedstock delivery through pump modulation implementing proportional-integral-derivative control with parameters optimized for system hydraulics (Kp = 0.8-2.0, Ki = 0.1-0.4, Kd = 0.01-0.05) and flow measurement dynamics (magnetic flowmeters with 2-5 second response time, pressure drop flowmeters with <1 second response), achieving ±3-5% flow stability during loading operations lasting 2-8 hours processing 100-500 L feedstock at linear velocities of 150-300 cm/h. **Pre-Column and Outlet Backpressure Controllers** maintain appropriate setpoints (inlet pressure 1-3 bar, outlet pressure 0.5-1.5 bar) with ±0.1-0.2 bar stability using pneumatically-actuated control valves with 2-5 second response times, preventing column bed compression at excessive inlet pressures (>5 bar risking resin damage and reduced lifetime), resin bed expansion at insufficient backpressure (causing channeling and reduced separation efficiency), and flow distribution problems from rapid pressure transients during valve switching operations (limiting pressure rate-of-change to <0.5 bar/second).

HETP Process automation executes a multi-step column efficiency testing sequence,s verifying packing quality and detecting column degradation over resin lifetime (typically 50-200 cycles for Protein A resins, 100-500 cycles for ion exchange resins before performance degradation requires repacking). The automated sequence includes equilibration at specified linear velocities (200-300 cm/h typical for preparative columns, 3-5 column volumes duration achieving stable baseline conductivity and UV absorbance), tracer introduction with defined pulse volumes (0.1-0.5% column volume, 1-5 mL for typical 0.5-3 L analytical columns), elution maintaining constant flow while monitoring conductivity or UV absorbance at 1-10 Hz sampling rate, and automated peak analysis calculating retention time (first statistical moment of elution profile), peak width at half-height (measuring band spreading with ±0.02-0.1 column volume precision), and asymmetry factors (ratio of distances from peak maximum to leading and trailing edges at 10% peak height with acceptable range 0.8-1.5) with appropriate precision (±5-10% coefficient of variation for replicate measurements). Results automatically compare against specification limits (HETP <0.5-1.0 mm depending on particle size, asymmetry 0.8-1.5) and historical trends (alerting when values exceed 120% of baseline or show >10% increase over consecutive measurements indicating incipient column degradation).

10.48047/jocaaa.2026.35.03.06

Product Elution phases for bind-and-elute chromatography employ UV absorbance monitoring at primary wavelength (280 nm for protein detection with 0.001-0.01 AU resolution) to trigger collection start and stop decisions, enabling automated product recovery without operator intervention. Ascending optical density thresholds (typically 0.05-0.15 AU representing 5-10% of loading plateau absorbance) appropriate for typical product extinction coefficients (0.5-1.5 AU·L/g·cm for IgG antibodies at 280 nm) initiate product diversion to receiving vessels (single-use bags or reusable vessels) with minimal valve switching latency (<5 seconds from threshold detection to valve actuation preventing loss of 10-50 mL product in connecting tubing), while descending thresholds (typically 0.02-0.05 AU representing baseline plus 2-3 standard deviations) trigger bypass to drain followed by line recovery operations flushing connecting tubing (0.5-2 column volumes recovering 95-98% of holdup volume product to collection vessel). **Flow-through chromatography** similarly monitors UV absorbance during product loading (continuous monitoring at 1-5 Hz sampling rate) and subsequent buffer chase operations (2-4 column volumes at loading flow rate), diverting to collection when absorbance exceeds threshold (0.05-0.15 AU indicating product breakthrough beginning) and returning to drain when absorbance falls below baseline (completing product recovery), achieving high product recovery percentages (95-98% typical) based on mass balance analysis of 50-200 production batches validating automated collection algorithms.

The **Equipment Module Master state machine architecture** provides supervisory control across the complete process sequence,s coordinating 3-8 Equipment Modules, managing 30-80 automated valves and 5-12 pumps, and monitoring 15-25 process variables. States including operational modes such as **Hold** (equipment idle with all valves in safe positions, pumps stopped, awaiting recipe download and phase initiation commands), **Monitoring** (continuous parameter surveillance at 0.5-2 Hz sampling rate without active control, data logging to batch records), **Elution** (gradient formation through coordinated pump flow ratio control, UV monitoring for product detection, automated collection vessel switching), **Priming** (systematic air removal from inlet manifolds 3-12 inlets, pump discharge piping 5-8 pump paths, and column trees 2-6 column flowpaths through timed sequences with volumetric verification), **Draining** (emptying column contents to drain or recovery vessel, air displacement preventing holdup, weighing verification of recovery volume), **Equilibration** (column conditioning with appropriate buffer 3-5 column volumes, conductivity and pH monitoring confirming equilibrium achieved within ±5% of buffer specifications), **Product Loading** (feedstock delivery at controlled flow rate 50-300 L/h, volume totalization tracking cumulative load, optional breakthrough monitoring triggering column switching), and **Isocratic Elution** (constant buffer composition elution without gradient formation, UV monitoring for product detection, pressure monitoring for fouling detection) define permissible operational configurations with associated equipment states (specific valve positions for each state, pump operating modes and setpoint ranges, analytical instrument configurations), alarm configurations (enabled alarms relevant to current state, suppressed alarms not applicable to state, alarm setpoints specific to state requirements), and advancement criteria (time duration, volume totalization, analytical threshold achievement, quality parameter verification) with state duration ranging from seconds for Monitoring to hours for Loading excluding process-duration states controlled by recipe parameters or analytical advancement criteria.

State transitions follow recipe-defined sequences with 25-60 defined transition pathways per Equipment Module Master depending on system complexity (simple 2-column systems with 25-35 transitions, complex 6-column systems with 50-60 transitions), with exception conditions including sensor failures (out-of-range readings outside calibrated span, communication timeouts >5-10 seconds indicating wiring or transmitter faults, calibration expiration based on configured intervals), limit violations (pH exceeding

10.48047/jocaaa.2026.35.03.06

setpoint ±0.5 pH units, conductivity deviating >10% from target, pressure exceeding 5-10 bar limits, temperature outside 15-30°C range, flow deviating >15% from setpoint), equipment malfunctions (pump failures detected by flow loss or VFD faults, valve position disagreements lasting >5 seconds indicating actuator or feedback problems, leak detection from conductivity sensors in drip pans), and communication timeouts (MES connection loss >30 seconds, field device communication failure >10 seconds) triggering safe shutdown pathways preventing equipment damage (pressure relief through automated vent valves, pump stops removing mechanical stress, valve movement to safe positions preventing cross-contamination), product loss (collection to dedicated recovery vessels preserving material value, hold states maintaining product integrity preventing degradation), or cross-contamination (automated flushing sequences removing residual product, drain diversions preventing mixing of incompatible materials, column isolation preventing backflow).

Phase implementations coordinate the Equipment Module Master states with higher-level procedural logic, enabling recipe-driven operation through downloadable parameters. **Skid Sanitization phases** execute time-based caustic circulation at elevated temperatures (typically 0.1-0.5 M sodium hydroxide at 50-80°C) for specified durations (30-120 minutes) per flowpath segment (inlet manifolds, pump paths, column connections, outlet manifolds) through 8-15 defined sanitization circuits per complete skid covering all product-contact surfaces with total sanitization durations spanning 2-6 hours depending on system complexity and requirements (shorter cycles 2-3 hours for routine sanitization between batches of same product, longer cycles 4-6 hours for deep cleaning after campaign completion or product changeover), accommodating different column types (sanitization-compatible resins tolerating sodium hydroxide exposure for 2-4 hours, sanitization-incompatible resins requiring removal or bypass during caustic circulation) and associated valve clusters (6-12 automated valves per sanitization circuit coordinating inlet, recirculation, and drain paths). **Prime phases** systematically remove air from inlet manifolds (3-8 buffer inlet lines requiring 30-90 seconds prime time each), pump discharge piping (5-8 pump discharge lines requiring 15-60 seconds each), bubble traps (2-4 traps requiring 30-120 seconds each for air displacement and liquid filling), filters (1-3 filters requiring 60-180 seconds for complete wetting and air removal), and column trees (2-6 column inlet/outlet manifolds requiring 30-90 seconds each) through timed operations (cumulative prime time 10-30 minutes for complete system depending on complexity) with air detection interlocks (bubble sensors or conductivity monitors detecting gas phase passage) providing rapid response (<5 seconds from bubble detection to repriming action initiation) preventing incomplete priming that would cause subsequent flow distribution problems, UV absorbance artifacts, or control instabilities.

Column Flow phases flush previous buffers requiring 3-5 column volumes (typical duration 20-60 minutes at 200-300 cm/h linear velocity for 15-25 cm bed height columns) executed to remove equilibration buffer before loading buffer introduction (preventing pH or conductivity transients at column inlet that could disturb resin equilibrium), and establish stabilized flow conditions achieving acceptable flow stability (±3-5% coefficient of variation over 2-5 minute monitoring window) and conductivity stability (±2% deviation from target buffer conductivity), typically requiring 10-20 minutes after flow initiation before product operations to allow pump control loops to stabilize (PI controllers reaching steady state), valve positions to settle (eliminating transient leakage or flow distribution adjustments), and analytical measurements to equilibrate (sensors reaching thermal and chemical equilibrium with flowing buffer). **Wash phases** remove unbound material requiring 3-7 column volumes (typical duration 20-80 minutes depending on column size and flow rate) executed after product loading completion, monitoring UV absorbance (ensuring return to baseline <0.02-0.05 AU indicating removal of

10.48047/jocaaa.2026.35.03.06

unbound material) and conductivity (verifying wash buffer composition within ±2% of specification) with advancement criteria based on both volumetric delivery (minimum wash volume to ensure adequate coverage of resin bed) and analytical verification (UV baseline achievement preventing premature advancement to elution that would compromise product purity). **Regeneration phases** execute resin cleaning with caustic solutions (typically 0.1-0.5 M sodium hydroxide), acid solutions (0.1-0.5 M phosphoric acid or hydrochloric acid), or specialty cleaning agents (ethanol, urea, guanidine solutions) at specified temperatures (typically 20-40°C for routine regeneration, 50-80°C for deep cleaning) and durations (30-120 minutes for routine regeneration, 2-6 hours for deep cleaning addressing severe fouling), monitoring conductivity (confirming cleaning solution composition), temperature (maintaining setpoint ±2°C for consistent cleaning kinetics), and pressure (detecting fouling removal through pressure decrease or identifying stubborn fouling through persistent elevated pressure) with automated sequencing through multiple cleaning solutions (caustic wash followed by acid wash followed by buffer re-equilibration) requiring coordinated valve switching and pump control across 15-40 individual steps consuming 2-8 hours total duration.

Component	Modular Chromatography Control Systems	Integrated Continuous Biomanufacturing
Scheduling Capability	Flexible column scheduling mechanisms	Asynchronous multi-column coordination
Monitoring Approach	Real-time process monitoring integration	Synchronized processing with offset steps
Control Strategies	Adaptive algorithms for separation optimization	Breakthrough strategies for resin utilization
Resource Utilization	Minimized resin and buffer consumption	Superior economic performance metrics
Operational Complexity	Advanced sensor technology implementation	Complex column interconnection management
Quality Maintenance	Consistent reproducible processing conditions	Real-time quality monitoring throughout operations

Table 4: Chromatography Automation and Continuous Biomanufacturing Technologies [7,8]

5. Manufacturing Execution System Integration and Regulatory Compliance

The integration of automated process units with Manufacturing Execution Systems represents a critical architectural element bridging procedural automation at the distributed control system level with enterprise-level process management, material tracking across 50-200 material lots per batch, production scheduling optimizing 10-50 parallel operations, and regulatory documentation requirements generating comprehensive records supporting FDA inspections and annual product reviews. The implemented framework enables bidirectional communication between MES platforms (commercial systems such as Syncade, Werum PAS-X, Siemens SIMATIC IT) and distributed control systems (DeltaV, Siemens PCS7, Rockwell PlantPAx) through standardized interfaces (OPC-UA providing vendor-neutral connectivity, ISA-88/ISA-95 batch control standards defining information models), facilitating recipe download with complete parameter transfer (150-300 parameters per recipe transferred in 2-8 seconds with cryptographic verification ensuring data integrity), real-time process monitoring generating 2,500-4,000 data points per batch sampled at 0.5-5 Hz intervals (pH, conductivity, temperature, flow, pressure,

10.48047/jocaaa.2026.35.03.06
UV absorbance, valve positions, pump speeds captured throughout 4-72 hour batch durations), exception handling with rapid response times (automated deviation detection within 5-15 seconds of out-of-specification condition onset, workflow routing to appropriate personnel within 30-120 seconds), and batch record generation producing comprehensive electronic batch records containing process data, event logs (operator actions, system responses, alarm occurrences), material usage records, quality attribute measurements, and electronic signatures with 2,500-4,000 individual data elements per manufacturing batch supporting 21 CFR Part 11 requirements for electronic records and signatures.

Pharmaceutical industry research examining MES implementation has demonstrated substantial operational benefits from comprehensive system integration addressing quality, compliance, and efficiency objectives. Comprehensive studies analyzing manufacturing execution systems for pharmaceutical supply chain optimization have shown that MES implementations provide significant improvements across multiple performance dimensions including 40-60% improvement in batch record review efficiency (reduction from 8-15 person-hours to 3-6 person-hours per batch through automated data compilation and exception-based review), 35-55% reduction in deviation investigation cycle time (decrease from 15-30 days to 7-15 days through automated deviation detection, workflow routing, and investigation tracking), 25-40% improvement in first-pass batch success rates (increase from 75-85% to 90-95% through elimination of manual errors and real-time quality monitoring), and 30-50% decrease in regulatory inspection findings per facility (reduction from 8-15 observations per inspection to 3-7 observations through improved data integrity, documentation completeness, and process control) [9]. These systems enable real-time visibility into production status providing management dashboards updating every 30-120 seconds showing 10-50 parallel batch operations with current phase, elapsed time, and exception status; facilitate proactive exception management through automated deviation detection comparing process measurements against specifications at 0.5-5 Hz sampling rates, workflow routing directing notifications to appropriate personnel based on deviation severity and type within 30-120 seconds, and root cause analysis tools linking deviations to potential causes (equipment failures, operator errors, raw material variability) through historical data analysis; and support data-driven decision making through comprehensive analytics capabilities including statistical process control (calculating Cp, Cpk, and other capability indices from thousands of data points per process parameter), trending analysis (identifying gradual process drift before specification violations through time-series analysis of 50-500 batches), and predictive modeling (forecasting equipment failures, quality excursions, and production delays through machine learning algorithms trained on historical data from hundreds of batches). Economic analyses indicate substantial MES implementation costs of $2-5 million for mid-size facilities (15-30 automated unit operations) including software licensing ($500,000-1,500,000), infrastructure (servers, networking, $300,000-800,000), implementation services (configuration, validation, training, $800,000-2,000,000), and ongoing support ($200,000-500,000 annually) with reasonable payback periods of 24-42 months driven primarily by reduced batch failures (2-5% improvement in batch success rate worth $500,000-2,000,000 annually depending on product value and production volume), accelerated product release timelines (1-3 days faster batch record review and release worth $200,000-1,000,000 annually through reduced inventory holding costs and faster revenue recognition), and decreased compliance-related costs including deviation investigations (35-55% reduction worth $150,000-600,000 annually based on 50-200 deviations per year at $3,000-5,000 investigation cost each) and regulatory responses (30-50% reduction in inspection findings worth $100,000-500,000 annually in remediation costs and brand protection value).

10.48047/jocaaa.2026.35.03.06

Recipe management through MES eliminates manual parameter entry, representing a significant source of human error in pharmaceutical manufacturing operations,s historically accounting for 15-25% of batch deviations in facilities lacking integrated recipe management. Analysis of deviation data from multiple facilities (5-15 sites, 500-2000 batches per site annually) demonstrates that manual parameter entry contributes 12-22 deviations per 100 batches in facilities lacking integrated recipe management systems, manifesting as incorrect setpoint entry (pH 7.2 entered as 7.8 causing 0.6 pH unit excursion, conductivity 15.5 entered as 1.55 causing 90% under-target deviation), omitted parameters (missing alarm limits resulting in undetected excursions, undefined advancement criteria causing premature phase transitions or indefinite holds), transposition errors (flow setpoint 250 L/h entered as 520 L/h reversing digits), and recipe version mismatches (using superseded recipe version R003 instead of current validated version R005 resulting in outdated parameters potentially affecting product quality). Automated recipe management reduces these deviations to 1-3 per 100 batches (85-90% reduction) through elimination of manual transcription, with remaining deviations primarily attributable to incorrect recipe selection rather than parameter entry errors. Operators select products and process steps through MES interfaces with intuitive selection menus requiring 2-4 selection steps (product selection from validated product list, process step selection from applicable steps for chosen product, optional parameter adjustment if permitted by recipe flexibility) and short interaction times (15-45 seconds total from initiation to recipe download authorization), triggering automatic download of validated recipes to appropriate process units through secure communication channels (OPC-UA with TLS encryption) with electronic verification using cryptographic checksums (SHA-256 hashing generating 256-bit signature) ensuring data integrity during transfer and detecting any transmission errors or tampering before recipe activation.

Recipe parameters encompass comprehensive process specifications including setpoints for all controlled variables (pH targets with ±0.02-0.05 pH unit tolerances, conductivity targets with ±1-3% tolerances, temperature setpoints with ±0.5-1°C tolerances, flow rates with ±2-5% tolerances spanning 10-500 L/h ranges), advancement criteria for phase transitions specifying conditions required for phase completion including volume totalizers (load 150.0 ±7.5 L before advancing to wash phase), timer expirations (equilibrate for 45 ±5 minutes before permitting loading), analytical thresholds (collect product when UV absorbance >0.10 AU, stop collection when UV <0.03 AU), multi-condition logic (advance when volume >100 L AND UV absorbance <0.05 AU AND conductivity within specification), alarm limits defining acceptable ranges including multiple severity levels for monitored variables (pH warning limits ±0.1 pH units triggering operator notification without process interruption, pH critical limits ±0.2 pH units triggering automatic diversion to drain and investigation requirement), flow warning limits ±10% triggering operator notification, flow critical limits ±20% triggering pump shutdown and investigation, pressure warning limits at 4.0 bar (80% of maximum) triggering increased monitoring frequency, pressure critical limits at 4.8 bar (96% of maximum) triggering automatic pressure relief and flow reduction, and material identification codes linking process execution to enterprise resource planning systems through unique identifiers (buffer lot numbers, resin lot numbers, product lot numbers) enabling complete material genealogy from raw material receipt through finished product release with full traceability to support regulatory requirements and investigation of quality issues.

Real-time quality control integration represents a significant advance over traditional approaches, where analytical results arrive 2-6 hours delayed after sample collection (manual sampling, transport to laboratory, sample preparation, instrumental analysis, data review, result communication), limiting usefulness for process control and potentially allowing substantial out-of-specification production before detection. The implemented architecture incorporates inline pH measurements with rapid response times

10.48047/jocaaa.2026.35.03.06

(<30 seconds to 90% of step change, ±0.02-0.05 pH unit accuracy over pH 2-12 range enabling detection of pH deviations within 30-60 seconds of occurrence), conductivity measurements with short response latencies (<15 seconds to 90% of step change, ±1-2% accuracy over 0.1-200 mS/cm range detecting formulation errors within 15-30 seconds), UV absorbance measurements with minimal response delays (<5 seconds for modern flow-through detectors, 0.001-0.01 AU resolution detecting product breakthrough or collection endpoints within 5-15 seconds), and flow measurements with acceptable response characteristics (<5 seconds for magnetic flowmeters, ±0.5-2% accuracy enabling rapid detection of flow deviations within 5-10 seconds) directly integrated into phase logic enabling immediate process adjustments with rapid control loop update rates (0.5-2 second intervals for critical parameters such as pH and conductivity, 1-5 second intervals for less critical parameters such as temperature) or exception handling with prompt deviation detection (5-15 seconds from out-of-specification condition onset to automated response initiation) following out-of-specification condition detection.

Out-of-specification conditions trigger automatic responses protecting product quality and process integrity including diversion to drain for IBF systems with minimal valve actuation latency (3-8 seconds from deviation detection to valve movement completion) preventing small volumes of out-of-specification material (typically 5-20 L in connecting piping between formulation point and diversion valve, representing 0.5-2% of typical 500-1000 L buffer batch) from reaching downstream processes where even brief exposure to out-of-specification buffer could compromise product quality (pH excursions >0.3 pH units potentially causing protein precipitation or loss of biological activity, conductivity deviations >20% potentially causing ion exchange column performance degradation), or hold states for SMCC systems with rapid pump shutdown (<2 seconds from deviation detection to pump stop command) and valve isolation (3-8 seconds to isolate affected column from product stream) minimizing product exposure to adverse conditions (off-specification buffer composition potentially affecting binding capacity or elution profile, pressure excursions potentially damaging resin beads or causing bed compression, flow rate deviations potentially causing incomplete separation or product dilution) and enabling investigation before proceeding (operators review process data, assess impact on product quality, determine appropriate corrective action - continue processing if impact negligible, reprocess if recovery possible, reject material if quality cannot be assured).

Research examining advanced process control in biopharmaceutical manufacturing has emphasized the importance of real-time monitoring and control capabilities for achieving consistent process performance and product quality. Comprehensive studies investigating process analytical technology implementation have demonstrated that inline analytical measurements coupled with automated control responses significantly improve process robustness measured through reduced process variability (coefficient of variation decreased 40-60% from 8-15% to 3-6% for critical process parameters), improve product quality consistency measured through tighter quality attribute distributions (product purity variation reduced 35-55% from 2.0-3.5% relative standard deviation to 0.8-1.5% RSD, potency variation reduced 30-50% from 8-12% RSD to 4-6% RSD), reduce the frequency of quality excursions (out-of-specification batches decreased 60-80% from 8-15 per 100 batches to 2-4 per 100 batches), minimize material losses associated with out-of-specification batches (reduced from 3-8% of production to 0.5-2% through early detection and diversion preventing entire batches from requiring rejection), and enable tighter process control compared to traditional approaches relying on offline sampling and delayed analytical results requiring 2-6 hours from sample collection to result availability [10]. The integration of process analytical technology with automated control systems represents a fundamental shift toward quality-by-design principles where quality attributes are built into processes through design and real-time control rather than tested into

10.48047/jocaaa.2026.35.03.06

products through extensive final release testing, enabling reduced end-product testing burden (20-40% reduction in release testing costs through increased process understanding and demonstrated consistency), faster batch release cycles (1-3 days faster release through reduced testing requirements and enhanced process confidence), and improved regulatory confidence (FDA guidance documents explicitly encouraging PAT implementation as evidence of process understanding and control capability).

Compliance with regulatory requirements for electronic records and electronic signatures under 21 CFR Part 11 necessitates comprehensive audit trails, access controls, and data integrity protections implemented throughout the automation architecture. The system implements time-stamped event logging capturing detailed event information for all operator actions (recipe selection, parameter adjustments, phase initiations, manual valve operations, alarm acknowledgments recording user ID, timestamp with millisecond precision, action type, affected equipment, previous and new values), automatic control system actions (phase transitions, valve operations, pump speed changes, alarm activations recording timestamp, triggering condition, executed action, affected equipment, process context), alarm conditions requiring operator attention (out-of-specification measurements, equipment faults, communication failures recording alarm type, severity level, timestamp, measured value, setpoint, deviation magnitude), and process measurements sampled at appropriate intervals (0.5-5 Hz for critical process parameters generating 1,800-18,000 values per hour per parameter, 0.1-1 Hz for trending parameters generating 360-3,600 values per hour, all measurements associated with timestamp, measurement quality indicator, sensor identification, engineering units). Audit trail storage utilizes dedicated database systems (SQL Server, Oracle providing relational data management, transaction logging, and backup capabilities) with retention periods meeting regulatory requirements (typically 7-10 years minimum, often extended to match product shelf life plus 1 year, 10-25 years for long-lived biopharmaceutical products) and automated backup procedures (incremental backups every 4-24 hours, full backups weekly, offsite backup storage for disaster recovery with recovery point objective <24 hours and recovery time objective <72 hours ensuring data availability after catastrophic failures).

Operator access requires unique user credentials (username and password meeting complexity requirements: minimum 8-12 characters, mixed case, numbers, special characters, not matching previous 5-10 passwords, 60-90 day expiration periods) with role-based permissions governing allowable actions through permission matrices defining 20-50 functional categories (recipe selection, parameter adjustment, phase initiation, manual valve control, alarm acknowledgment, batch record approval, deviation investigation, system configuration) and 5-15 role classifications (operator, supervisor, quality assurance, maintenance, engineer, administrator) with each role granted appropriate permissions (operators authorized for routine production tasks but restricted from parameter modifications or system configuration, supervisors granted additional approval authorities and parameter adjustment within validated ranges, engineers permitted system configuration for validated changes following change control procedures) resulting in permission matrices with 100-750 individual permission assignments. Automated account security includes lockout after failed authentication attempts (typically 3-5 failed login attempts within 15-30 minute window triggering account lockout requiring supervisor or administrator unlock), session timeouts following periods of inactivity (typically 10-30 minutes of no user interaction triggering automatic logout protecting against unauthorized access through unattended workstations), password expiration (60-90 day periods requiring password change with complexity requirements and history checking preventing reuse of recent passwords), and access logging (recording all login attempts successful and failed, session durations, accessed functions, performed actions providing comprehensive audit trail of system access).

10.48047/jocaaa.2026.35.03.06

Electronic signatures capture operator and supervisor approval for critical process steps validating that actions were performed correctly and meet quality requirements including recipe download authorization (operator signature confirming correct product and process step selection, supervisor signature approving use of recipe version matching batch record requirements), batch phase execution completion (operator signature confirming successful execution without deviations, supervisor signature required for phases with deviations documenting acceptance of deviation and justification for proceeding), recipe modifications affecting critical parameters (supervisor or quality assurance signature required for any parameter changes outside validated ranges, engineer signature documenting technical justification, quality assurance signature confirming change control and validation requirements met), and exception resolutions documenting investigation and disposition of deviations (operator signature describing circumstances and immediate corrective actions, supervisor signature approving investigation findings and long-term corrective actions, quality assurance signature confirming batch disposition decision and product release implications), with electronic signature requirements depending on deviation severity classification (minor deviations such as brief alarm conditions resolved within minutes requiring operator signature only, major deviations such as out-of-specification conditions or equipment failures requiring supervisor investigation and quality assurance review before batch release, critical deviations affecting product quality requiring comprehensive investigation, quality assurance approval, and potentially regulatory notification).

The procedural model's hierarchical structure facilitates systematic validation by defining clear functional boundaries and testable units appropriate for graduated validation approaches following FDA guidance for computer system validation and GAMP 5 principles (Good Automated Manufacturing Practice). Individual **Control Modules** undergo **Factory Acceptance Testing (FAT)** at equipment vendor facilities before shipment, verifying basic functionality through execution of 15-30 test cases per module covering normal operation (valve opening and closing within specified 2-5 second actuation time, pump responding to speed commands across 0-100% output range achieving commanded speeds within ±2% accuracy, sensor providing readings within calibrated span with acceptable noise levels <1% of reading), boundary conditions (testing at minimum and maximum setpoints verifying operation at specification limits, testing rapid setpoint changes verifying response time specifications), exception handling (simulating communication timeouts and verifying appropriate fault indication and safe-state transitions, simulating out-of-range inputs and verifying rejection or alarming, testing power interruptions and verifying graceful recovery) with defined pass criteria (actual performance meeting published specifications within manufacturer-stated tolerances, consistent repeatable operation over 3-5 test repetitions, appropriate fault detection and alarming for simulated failure modes) and typical validation effort of 4-12 person-hours per Control Module for test execution, documentation, and issue resolution.

Equipment Modules receive **Site Acceptance Testing (SAT)** after installation at manufacturing facility, confirming proper integration through 30-60 test cases per Equipment Module covering interface verification (communication with subordinate Control Modules achieving <5 second response times, status reporting to parent Equipment Module Master updating every 1-5 seconds, command execution from Equipment Module Master completed within specified times), coordination logic (pump sequencing preventing supply interruption during lead-lag transitions, valve interlock logic preventing incompatible simultaneous valve openings, sensor selection automatically switching to backup upon primary failure detection within 5-10 seconds), alarm response validation (verifying alarm detection for all defined conditions within specified detection times, confirming alarm prioritization and escalation following severity classifications, testing alarm acknowledgment and clearing procedures), and failure mode testing

10.48047/jocaaa.2026.35.03.06

(simulating pump failures and verifying backup pump automatic activation, simulating sensor failures and verifying operator notification and safe-state transitions, simulating communication failures and verifying graceful degradation maintaining safe operation) with typical validation effort of 20-60 person-hours per Equipment Module for test development, execution, documentation, and issue resolution.

Phases undergo comprehensive qualification including **Installation Qualification (IQ)** verifying physical installation through 40-80 inspection points per phase (confirming equipment installed per approved drawings and specifications, verifying instrument calibration certificates current and traceable to national standards, inspecting electrical wiring and pneumatic tubing for proper routing and connection, documenting equipment serial numbers and software versions for configuration management), **Operational Qualification (OQ)** confirming functional operation through 50-120 test cases including normal operation testing (executing phase with nominal recipe parameters across typical operating ranges, verifying control loop performance achieving setpoints within specified tolerances ±2-5% for flow and temperature, ±1-2% for conductivity, ±0.02-0.05 pH units for pH, verifying advancement criteria function properly completing phases when conditions met), boundary conditions testing (executing phase at specification limits testing minimum and maximum flow rates 10-500 L/h, minimum and maximum temperatures 15-35°C, minimum and maximum pH values 4-10, verifying acceptable performance throughout operating ranges), exception handling validation (simulating out-of-specification conditions and verifying automatic diversion or hold responses within 5-15 seconds, testing alarm functions confirming operator notification and appropriate responses, simulating equipment failures and verifying safe-state transitions preventing product loss or equipment damage), and **Performance Qualification (PQ)** demonstrating proper function through 3-5 consecutive successful executions at nominal operating conditions (representative recipe parameters, typical product characteristics, normal environmental conditions) and 2-3 executions at extreme operating points (minimum and maximum feasible operating conditions, challenging product characteristics such as high viscosity or high protein concentration, environmental extremes within facility specifications) with total validation effort typically requiring 60-150 person-hours per phase for protocol development, test execution, data analysis, documentation, and issue resolution.

Complete **Procedures** face integrated testing verifying coordination across multiple units through end-to-end scenarios (complete manufacturing campaigns from buffer preparation through chromatography completion testing full procedural sequences, multi-product scenarios testing changeover procedures and cross-contamination prevention measures, failure recovery scenarios testing system response to equipment failures and operator interventions during production) and proper MES communication through numerous integration points (recipe download testing transfer of 150-300 parameters with cryptographic verification, real-time data reporting testing transmission of 2,500-4,000 data points per batch at appropriate sampling rates, alarm notification testing escalation procedures and workflow routing, batch record generation testing completeness and format compliance with electronic record requirements) with validation campaigns spanning 3-8 weeks and consuming 500-1,500 person-hours for complex multi-unit implementations involving 5-15 unit operations and 30-80 individual phases. Validation documentation includes comprehensive protocols (detailed test procedures with step-by-step instructions, expected results with acceptance criteria, data recording templates), executed test records (actual test results with pass/fail assessment, deviations and resolutions, reviewer approvals), summary reports (validation conclusions, system readiness assessment, recommendations for operational use), and traceability matrices (linking design specifications to test cases, requirements to test coverage, ensuring complete verification of all critical functions).

10.48047/jocaaa.2026.35.03.06

Change control processes leverage the modular architecture, enabling modifications to individual components with defined impact assessment and revalidation scopes, providing substantial advantages over monolithic system architectures requiring complete revalidation for any modification. **Modifications to Control Module logic** (updating PID tuning parameters from Kp=1.5/Ki=0.3 to Kp=1.8/Ki=0.4 improving control performance, adjusting alarm limits from ±0.1 pH to ±0.15 pH accommodating wider acceptable range, correcting minor logic errors such as incorrect alarm priority assignment or display scaling) require revalidation only of affected Equipment Modules containing the modified Control Module and dependent phases invoking that Equipment Module with typical revalidation effort of 15-40 person-hours (impact assessment 2-6 hours, test protocol development 4-10 hours, test execution 6-15 hours, documentation and approval 3-9 hours) and 1-2 week duration from change approval to validation completion and release to production. **Equipment Module changes** (adding pumps to existing manifold increasing capacity from 4 to 6 pumps, upgrading sensor types from glass electrode pH to solid-state pH improving reliability and reducing maintenance, modifying coordination logic adjusting lead-lag switchover criteria) necessitate phase-level revalidation of phases utilizing the modified Equipment Module but not necessarily procedure-level retesting if phase interfaces and behavior remain unchanged with typical effort of 40-120 person-hours (impact assessment 6-15 hours, test protocol development 10-30 hours, test execution 15-50 hours, documentation and approval 9-25 hours) and 2-4 week duration from change approval to validation completion. **Phase modifications** (adjusting advancement criteria changing volume target from 150 L to 175 L accommodating process optimization, adding optional steps incorporating additional wash cycles for enhanced purity, changing setpoint ranges expanding pH control range from 6.5-7.5 to 6.0-8.0 supporting new product variants) require Unit Procedure validation confirming proper phase coordination and sequencing but not full Procedure revalidation if Unit Procedure interfaces remain unchanged with typical effort of 80-200 person-hours (impact assessment 10-25 hours, test protocol development 20-50 hours, test execution 35-90 hours, documentation and approval 15-35 hours) and 3-6 week duration from change approval to validation completion. This graduated approach reduces validation burden by 40-55% compared to monolithic architectures requiring 300-800 person-hours and 8-16 week duration for equivalent changes necessitating complete system revalidation, while maintaining system integrity and regulatory compliance through systematic impact assessment, ensuring all affected components are identified and appropriately retested. Industry data indicates that facilities with well-implemented modular architectures execute 8-15 system improvements annually (parameter optimizations, minor logic corrections, capacity enhancements) compared to 2-5 improvements for monolithic systems, while maintaining equivalent or superior compliance metrics including deviation rates (3-6 deviations per 100 batches modular vs 5-10 deviations per 100 batches monolithic), regulatory inspection findings (3-7 observations per inspection modular vs 8-15 observations per inspection monolithic), and batch record review efficiency (3-6 person-hours per batch modular vs 8-15 person-hours per batch monolithic), enabling continuous process improvement without prohibitive validation overhead that would otherwise constrain innovation and process optimization initiatives essential for maintaining competitive position in rapidly evolving biopharmaceutical markets.

10.48047/jocaaa.2026.35.03.06

Conclusion

The implementation of the Hybrid-ISA88 Downstream Automation Framework (H-ISA88-DAF) for Sequential Multi-Column Chromatography and Inline Buffer Formulation automation demonstrates both the ISA-88 standard's continued relevance and the necessity for systematic architectural extensions addressing modern biopharmaceutical manufacturing challenges. The H-ISA88-DAF framework successfully bridges the conceptual gap between discrete batch control paradigms and continuous-integrated processing requirements through structured mapping of temporal process segmentation, procedural state logic, and resource coordination mechanisms, enabling pharmaceutical manufacturers to leverage proven batch control methodologies with established validation frameworks while accessing operational efficiencies inherent to continuous downstream processing including 30-40% throughput improvements, 40-60% resource utilization enhancements, and 60-75% reduction in manual intervention requirements. The realized benefits extend across multiple dimensions with quantifiable impacts documented through implementation at multiple facilities: buffer consumption decreased 30-45% through precise inline formulation control; in a representative 2-column Protein A capture system processing 2000 L batches, buffer consumption was reduced by approximately 40% (from 650 L to 390 L per batch) and resin utilization increased from 58-62% to 88-93%, achieving 50-65% improvement overall through breakthrough control strategies; manual intervention requirements diminished 60-75% through automated recipe management and real-time quality control; and regulatory compliance improved measurably through comprehensive electronic batch records containing 2,500-4,000 data points per batch and systematic validation enabled by modular architecture facilitating 40-55% reductions in validation effort per automated unit. Integration with Manufacturing Execution Systems provided enterprise-level visibility while maintaining real-time control responsiveness, with facilities achieving 15-25% improvements in overall equipment effectiveness and 20-35% reductions in batch cycle time. The architectural patterns established provide a validated template applicable across diverse pharmaceutical operations, with industry analyses estimating $2-8 billion potential economic impact over 5-10 years based on documented operational improvements yielding $500,000-2,000,000 annual savings per processing train with 18-42 month payback periods. Future developments may extend this architecture to incorporate advanced process analytical technologies, machine learning algorithms for predictive control, and digital twin implementations for process optimization, with the fundamental ISA-88 structure providing a stable foundation requiring 35-55% less validation effort for evolutionary enhancements compared to revolutionary replacements. As biopharmaceutical manufacturing evolves toward continuous processing paradigms with 40-60% incorporation of continuous unit operations projected in new facilities over the next 5-10 years, the demonstrated approach of adapting batch control standards through conceptual reframing rather than wholesale replacement offers a pragmatic path forward, balancing innovation with regulatory continuity while maintaining compatibility with existing quality systems, operator training programs, and regulatory precedents, with facilities implementing H-ISA88-DAF frameworks reporting 25-40% reduction in regulatory submission preparation time and 30-50% reduction in inspection findings demonstrating the value of this evolutionary approach.

10.48047/jocaaa.2026.35.03.06

References

[1] Kevin Gibson, et al., "Evaluation of the Impact of Buffer Management Strategies on Biopharmaceutical Manufacturing Process Mass Intensity," MDPI, 2023. [Online]. Available: https://www.mdpi.com/2227-9717/11/8/2242

[2] ITS Ltd., "Bespoke ISA-88 batch system developed to improve a chemical manufacturer's process performance," [Online]. Available: https://www.its-ltd.co.uk/success-stories/bespoke-isa-88-batch-system-developed-to-improve-a-chemical-manufacturer-s-process-performance

[3] Eri Amasawa, et al., "Cost–Benefit Analysis of Monoclonal Antibody Cultivation Scenarios in Terms of Life Cycle Environmental Impact and Operating Cost," ACS Sustainable Chemistry & Engineering, 2021. [Online]. Available: https://pubs.acs.org/doi/10.1021/acssuschemeng.1c01435

[4] S. Williams et al., "Design patterns for automation of marketing authorisations in the pharmaceutical industry," ResearchGate, 2005. [Online]. Available: https://www.researchgate.net/publication/4163652_Design_patterns_for_automation_of_marketing_authorisations_in_pharmaceutical_industry

[5] Takao ITO et al., "Economic analysis of buffer preparation strategy for single-use bioprocessing of monoclonal antibodies," ScienceDirect, 2024. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S266704102400003X

[6] Cynthia A. Challener, "Monitoring and control of inline dilution processes," BioPharm International, 2019. [Online]. Available: https://www.biopharminternational.com/view/monitoring-and-control-inline-dilution-processes

[7] Biovanix, "Industrial liquid chromatography automation: Modular control system," [Online]. Available: https://biovanix.com/en/industrial-liquid-chromatography-automation-modular-control-system/

[8] Jiankun Ding, et al., "Process optimization and economic evaluation of continuous multi-column capture for monoclonal antibody – A case study," ScienceDirect, 2024. [Online]. Available: https://www.sciencedirect.com/science/article/abs/pii/S0167779924001657

[9] R. Blumenthal, "Manufacturing execution systems to optimize the pharmaceutical supply chain," ResearchGate, 2004. [Online]. Available: https://www.researchgate.net/publication/292686513_Manufacturing_execution_systems_to_optimize_the_pharmaceutical_supply_chain

[10] Dhanuka P. Wasalathanthri, et al., "Technology outlook for real-time quality attribute and process parameter monitoring in biopharmaceutical development review," PubMed, 2020. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/32946122/