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Research Article

Current Advances and Challenges in Pharmaceutical Formulation Development and Manufacturing: A Comprehensive Review for Industry Applications

Seyyed Amir Hosseini*

Department of Cellular and Molecular Biology, Islamic Azad University, Kermanshah, Iran

Abstract

Pharmaceutical formulation development and manufacturing have evolved rapidly with the advent of nanotechnology-enabled delivery, biopharmaceuticals, continuous manufacturing, and data-driven quality systems. This review synthesizes the state-of-the-art across formulation science and production technologies, with emphasis on industry adoption, regulatory expectations, and practical barriers. We discuss nano- and micro-structured drug products, patient-centric and long-acting designs such as implantable depots and microneedle patches, lyophilization and stabilization of biologics including monoclonal antibodies and vaccines, and digital design-of-experiments under Quality-by-Design (QbD). On the manufacturing side, we examine continuous processing for solid oral dosage forms, Process Analytical Technology (PAT) integrated with real-time monitoring, automation and robotics in aseptic filling lines, and technology transfer from lab to commercial scale. Persistent challenges include material variability from natural excipients, scale-up/scale-out complexities in multiphase systems, regulatory compliance amid evolving FDA/EMA guidelines, cost-to-value trade-offs in personalized medicine, and sustainability concerns like waste generation in solvent-based processes. Critically, we highlight how these challenges can lead to delays in tech-transfer or increased failure rates, as evidenced by recent industry reports from companies like Pfizer and Novartis. In addition to summarizing scientific advances, this review aims to provide practical insights for researchers and industry stakeholders by mapping opportunities against known limitations and regulatory expectations. The inclusion of recent case studies, such as lipid nanoparticle scaling for mRNA vaccines, and decision frameworks is intended to support both academic and industrial audiences. Actionable recommendations and future directions—AI-augmented development for predictive modeling, model-informed control strategies, and green chemistry principles—are proposed to accelerate reliable, affordable, and resilient supply, drawing from 2024–2025 trends in Pharma 4.0.

Keywords

Pharmaceutical Formulation, Drug Delivery, Biologics, Nanotechnology, Continuous Manufacturing, QbD, PAT, Regulatory Science

*Correspondence: Seyyed Amir Hosseini (seyedamirhosseini1100@gmail.com)

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1. Introduction

Formulation science translates an active pharmaceutical ingredient (API) into a safe, effective, and manufacturable drug product. [28] Modern pipelines feature poorly water-soluble small molecules, complex peptides and proteins, cell and gene therapies, and vaccines—each presenting unique stability and delivery hurdles. In parallel, manufacturing is shifting from traditional batch paradigms to data-rich, intensified, and often continuous processes. Regulators encourage scientific understanding and risk management through Quality-by-Design (QbD) and Process Analytical Technology (PAT). [2, 7].

However, this shift is not without risks; for instance, variability in raw materials can amplify failure rates during scale-up, as seen in recent biopharma attrition challenges. [1, 8, 23].

This review integrates scientific advances and pragmatic industrial considerations. We focus on technologies with demonstrated translational value, highlight regulatory expectations, and map challenges that commonly derail timelines and tech-transfer. Where possible, we provide decision frameworks and tables that can be adapted within corporate development playbooks, incorporating critical analysis of limitations and opportunities.

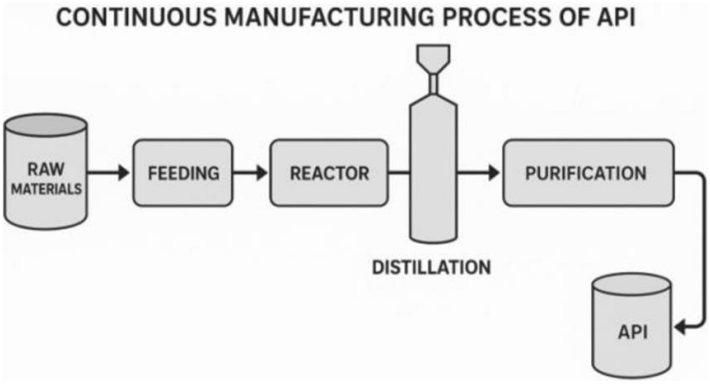

Figure 1. *Process flow diagram for continuous pharmaceutical manufacturing of an API (created by author, CC0).*

2. Methodology of Literature Review

We surveyed peer-reviewed literature, pharmacopeial chapters, and major regulatory guidelines from 2005–2025. Databases included PubMed, Scopus, and Web of Science. Priority was given to consensus documents (e.g., ICH Q8–Q12), FDA/EMA guidances, and industrial case reports. [4, 7, 9, 10] Articles were screened for (i) relevance to formulation or manufacturing innovation, (ii) demonstrated or plausible industry adoption, and (iii) clarity on quality and regulatory implications. Items were thematically coded to produce the synthesis below. To ensure currency, we incorporated recent reviews from 2024-2025 on trends like AI in drug delivery and sustainable manufacturing. [24-27].

3. Advances in Formulation Development

3.1. Nanotechnology-enabled Systems

Table 1. *Comparative Overview of Nanoparticle Platforms in Pharmaceutical Formulation Development and Manufacturing: Strengths, Key Risks, and Industrial Scale-Up Considerations [27].*

Platform	Strengths	Key Risks	Scale-Up Notes
Liposomes/LNPs	Biocompatible; versatile cargo	Oxidation; fusion; leakage	Microfluidic mixing; solvent removal
Polymeric NPs	Controlled release; targeting	Residual solvents; burst release	Emulsion/precipitation; PAT for size
SLN/NLC	High load for lipophilic APIs	Polymorphic transitions	Hot/cold homogenization; DSC control
Nanosuspensions	Simple composition	Crystal growth; Ostwald ripening	Wet media milling; stabilizer screening

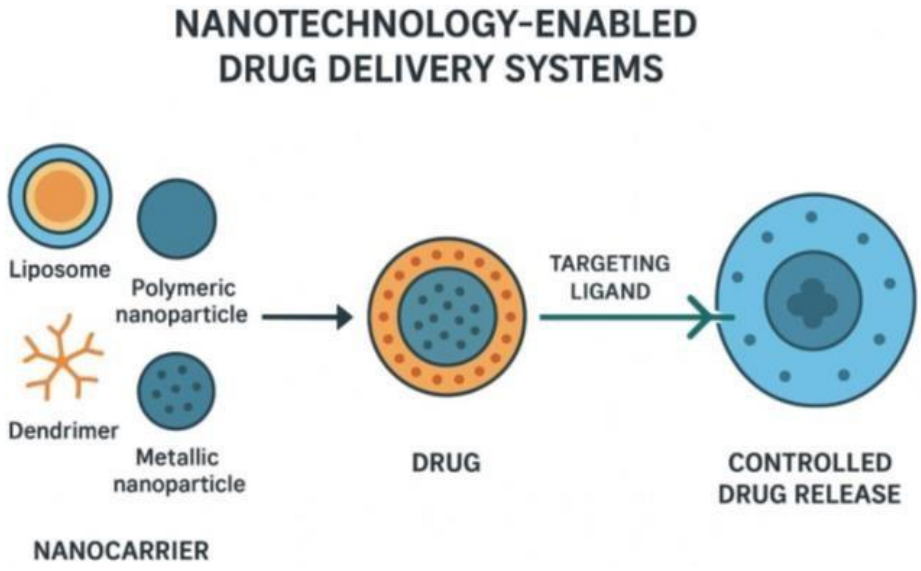

Figure 2. *Nanotechnology-enabled drug delivery systems. (created by author, CC0).*

Engineered carriers (liposomes, SLNs/NLCs [19], polymeric nanoparticles, dendrimers, nano-suspensions)[18] address solubility, permeability, and targeting. Control over size, zeta potential, and surface ligands tunes biodistribution and clearance. For oncology, long-circulating liposomes reduce off-target toxicity; for vaccines, lipid nanoparticles (LNPs) enable nucleic-acid delivery. [27] Key risks include physical instability (aggregation/fusion), excipient reactivity (e.g., polysorbate degradation), and scale-up complexity of high-shear or microfluidic processes. [13] Critically, while these systems enhance bioavailability, their environmental impact (e.g., nanoparticle persistence) remains understudied, posing sustainability challenges.

3.2. Formulating Biopharmaceuticals

Proteins and nucleic acids demand control of pH, ionic strength, and interfacial stresses. Stabilization leverages sugars (trehalose, sucrose), amino acids (arginine), buffers (histidine, acetate), and surfactants (polysorbates or poloxamers). Lyophilization remains vital for long-term stability, with cycle design guided by collapse temperature and critical formulation attributes. [15] For viral vectors and mRNA, low-temperature storage, chelators, and antioxidant strategies mitigate hydrolysis and oxidation. A key challenge in 2025 is high-concentration formulations for subcutaneous delivery, where viscosity and aggregation can hinder injectability, as highlighted in recent analyses. [14, 24].

3.3. Patient-centric and Long-acting Designs

Orally disintegrating tablets, mini-tablets, taste-masked liquids, and abuse-deterrent formulations improve adherence across special populations. Long-acting injectables (LAIs), in situ forming depots, and implants smooth exposure, reduce clinic visits, and support outcomes-based contracts. Digital companions (ingestible sensors, smart packaging) can further support persistence and real-world data collection. However, patient adherence remains variable, with studies showing up to 50% non-compliance in chronic therapies, underscoring the need for personalized designs.

3.4. Solid-state Engineering & Amorphous Systems

Polymorph selection, salt/cocrystal formation, and amorphous solid dispersions (ASDs) enhance developability of BCS II/IV molecules. [11, 23] Risk management focuses on physical stability (recrystallization), moisture uptake, and process-induced transformations. Hot-melt extrusion and spray-drying are dominant ASD routes; inline spectroscopies (NIR/Raman) enable real-time verification of drug dispersion. [12, 16] Recent innovations include multifunctional excipients to mitigate recrystallization risks. [27].

3.5. Sterile/Parenteral and Lyophilized Products

Aseptic processing demands robust container–closure integrity and control of particulate matter. For lyophilized products, annealing, controlled nucleation, and primary drying optimization reduce cycle time while preserving cake quality. Single-use technologies (SUT) minimize cross-contamination, but require extractables/leachables (E&L) risk assessments. Challenges include E&L from plastics, which can interact with biologics, leading to immunogenicity risks.

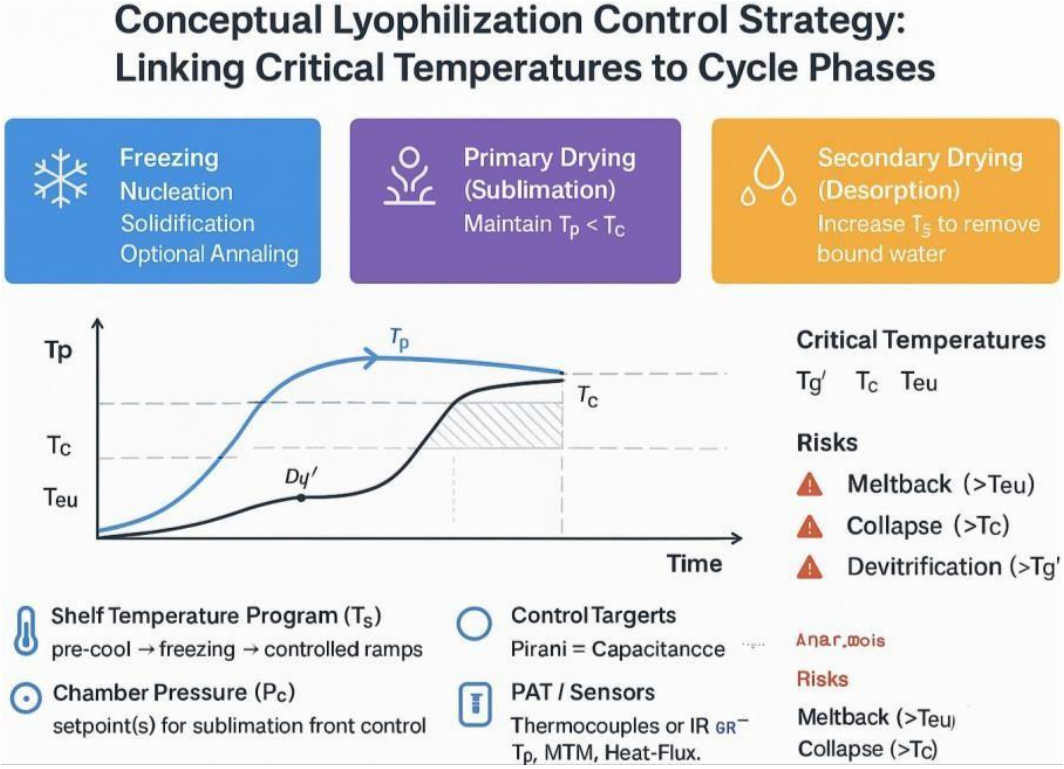

Figure 3. *Conceptual lyophilization control strategy linking critical temperatures to cycle phases. (created by author, CC0).*

Schematic: Lyophilization Cycle Control
1) Freezing → 2) Annealing → 3) Primary Drying → 4) Secondary
(Tc, ice) (crystal size) (sublimation; Tshelf/Pchamber) Sensors: T, P, impedance; Design targets: Tg', Tc, Rp

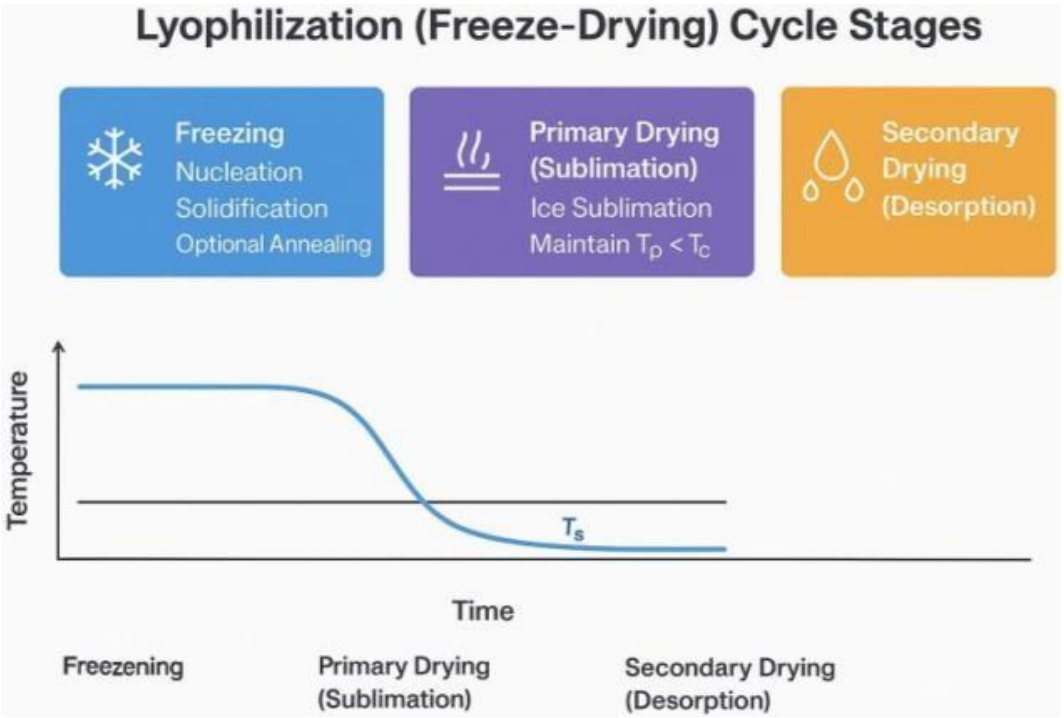

Figure 4. *Lyophilization (freeze-drying) cycle stages (created by author, CC0).*

4. Advances in Manufacturing Technologies

4.1. Continuous Manufacturing

Figure 5. Flowchart of continuous pharmaceutical manufacturing routes. (created by author, CC0).

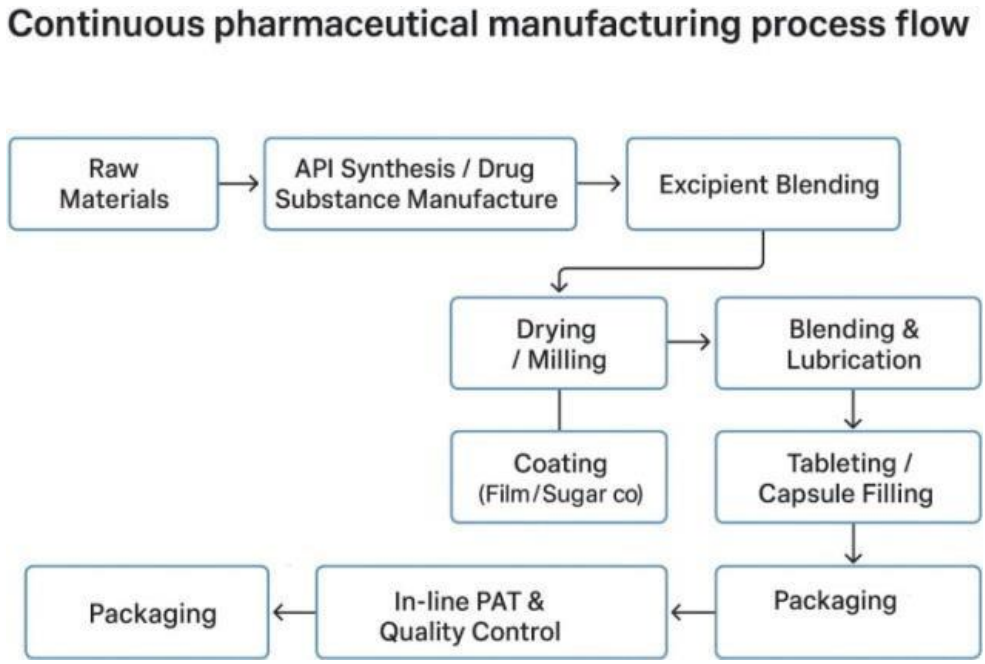

Figure 6. Continuous pharmaceutical manufacturing process flow (created by author, CC0).

Continuous manufacturing (CM) integrates feeding, blending, granulation, tableting, and coating with feedback control. Benefits include reduced variability, smaller footprints, and faster release via real-time release testing (RTRT). Adoption hinges on process understanding, residence time distribution (RTD) modeling, and robust diversion strategies during disturbances. While CM reduces waste, initial investment costs can be prohibitive, as noted in sustainability case studies. [5, 8, 11].

Table 2. Comparative Attributes of Batch versus Continuous Manufacturing in Pharmaceutical.

Attribute	Batch	Continuous
Scale strategy	Scale-up	Scale-out/intensification
Attribute	Batch	Continuous

Attribute	Batch	Continuous
Quality control	End-product testing	Inline PAT & RTRT
Footprint	Larger	Compact
Changeover	Long	Short
Disturbance handling	Rework/discard	Automated diversion

Formulation: Strategies, Quality Control, and Operational Considerations [5, 8].

4.2. Process Analytical Technology (PAT)

PAT provides real-time insight into critical quality attributes (CQAs). Common tools include NIR for blend uniformity, Raman for polymorph, focused beam reflectance measurement (FBRM) for particle size, [17] and mass/heat balances for CM state estimation. Multivariate statistical process control (MSPC) enables drift detection and proactive adjustments. Integration with AI enhances predictive capabilities, but data overload remains a challenge. [8,10].

4.3. QbD & Digital Design-of-Experiments

QbD couples prior knowledge with structured experimentation and modeling to define the design space. Digital DoE with Bayesian optimization or Gaussian processes reduces runs while mapping nonlinear responses. Model-based control strategies (MPC) use first-principles and data-driven models to maintain product quality under variability. Recent QbD applications in rethinking pharma underscore its role in reducing R&D costs. [23].

4.4. Automation, Robotics & 3D Printing

Robotic aseptic filling, automated guided vehicles, and closed-loop environmental monitoring increase throughput and compliance. Additive manufacturing enables personalized doses and polypills; current barriers include material libraries, printer qualification, and regulatory pathways. Pharma 4.0 case studies show automation reducing human error by up to 80%.

5. Regulatory Landscape & Quality Systems

Global regulators converge on science- and risk-based frameworks. ICH Q8–Q10 define development and quality systems; Q11 addresses drug substance;[3] Q12 facilitates post-approval change management; Q13 covers CM, and Q14 addresses analytical method development. [1, 6] FDA's Emerging Technology Program (ETP) supports novel platforms; EMA provides reflection papers and CM guidance aligned to ICH. Successful dossiers articulate product/platform knowledge, control strategies, and lifecycle change management, enabling reliance on RTRT and established conditions. However [21, 22], harmonization gaps between regions can delay approvals. [7-11].

6. Industry Case Studies

6.1. CM for Solid Oral Products

Commercial CM lines demonstrate hours-to-release timelines with consistent assay and content uniformity. RTD-based diversion policies and PAT-anchored RTRT underpin regulatory acceptance. For example, MSD's 2024 dataset from a CM line captured 300 million data points over 120 hours, revealing variability in 75 process parameters and enabling predictive modeling to reduce downtime by 20%. [8, 9, 11].

6.2. Liposomal Oncology Products

Liposomal doxorubicin and other nano-enabled therapies illustrate toxicity reduction via altered biodistribution; manufacturing requires tight control of particle size and encapsulation efficiency. A 2025 Roche case with integrated CM for a drug substance/product route achieved 30% efficiency gains but highlighted challenges in equipment integration. [8].

6.3. High-concentration mAb Formulations

Viscosity management (co-formulants, pH/ionic strength optimization) and container interactions are central for prefilled syringes and autoinjectors. Recent challenges include aggregation in high-concentration mAbs, with 2025 analyses showing up to 15% loss in stability during storage, mitigated by novel excipients. [24].

7. Cross-cutting Challenges

Table 3. Key Risks in Pharmaceutical Formulation Development and Manufacturing: Root Causes, Mitigation Strategies, and Decision Support Tools.

Risk	Root Cause	Mitigation	Decision Aid
Physical instability	Phase transitions; moisture	Excipient screening; packaging	Stress maps; isotherms
Scale-up variability	Flow/heat transfer changes	Dimensionless scaling; PAT	RTD models; DoE
Regulatory delays	Insufficient prior knowledge	QbD dossier; ETP engagement	Established conditions
Supply chain	Single-source excipients	Dual sourcing; SUT strategy	Risk registers; FMEA
Sustainability	Solvent/energy intensity	Green metrics; intensification	Life-cycle assessment

Critically, these challenges are interconnected; for instance, supply chain disruptions in 2025 could exacerbate sustainability issues, with excipient shortages driving up costs by 10-20%.[20]

8. Future Perspectives & Opportunities

AI/ML will increasingly power formulation screening (e.g., ASD polymer selection), predictive stability (Arrhenius-plus ML residuals), and soft sensors for PAT. Model-informed product and process development (MIPD/MIDD) can bridge pharmacometrics and manufacturing design. Sustainability priorities—benign solvents, energy-lean drying, circular single-use—will shape portfolio choices, especially with projected $14B excipient market growth by 2033. Emerging trends include nanoparticle-based techniques for advanced formulations and Pharma 4.0 for real-time digital twins. However, challenges like AI bias in predictive models and high R&D costs ($2.23B per asset) must be addressed through collaborative ecosystems. Finally, workforce upskilling in data science and automation is foundational to realize these gains. [8].

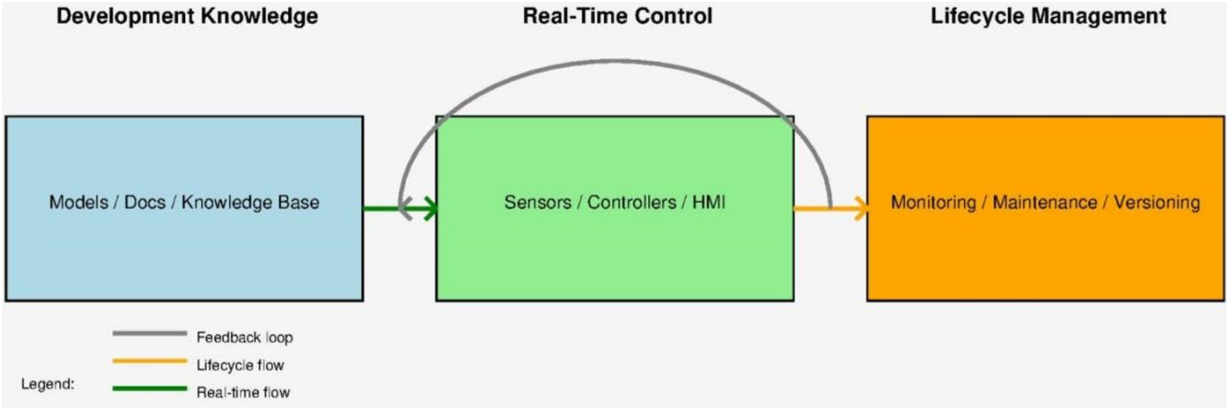

Figure 7. Conceptual data flow linking development knowledge to real-time control and lifecycle management. (created by author, CC0).

Data-Enabled Development and Manufacturing (Concept Map)

Knowledge Graphs ⟶ Digital DoE ⟶ Mechanistic + ML Models ⟶ PAT Soft Sensors ⟶ MPC/RTRT ⟶ Deviation Prediction & CAPA [8, 11].

9. Conclusion

Formulation and manufacturing are converging into an integrated, model-informed discipline. Companies that operationalize QbD, embrace PAT and CM, and build digital capabilities can compress timelines, elevate quality, and improve affordability. Strategic attention to stability science, tech-transfer, and regulatory engagement remains decisive for success, especially amid

2025's productivity challenges in biopharma. [1, 9, 23].

Abbreviations

QbD	QbD Quality-by-Design
PAT	Process Analytical Technology
RTRT	Real-Time Release Testing
MPC	Model Predictive Control

Author Contributions

Seyyed Amir Hosseini is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The author declares no conflicts of interest.

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