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DIGITAL TWINS IN PHARMACEUTICAL MANUFACTURING: A SCOPING REVIEW

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ABSTRACT

Digital twins offer a paradigm for real-time, predictive, and adaptive control in pharmaceutical manufacturing. Their relevance has increased with the expansion of continuous manufacturing, Process Analytical Technology, and model-informed quality assurance, but their adoption remains uneven and conceptually fragmented. This scoping review maps the extent, range, and nature of research on digital twins in pharmaceutical manufacturing from 2017 to 2026. The review focuses on process modeling, PAT integration, validation strategies, regulatory positioning, and applications related to real-time release testing. A scoping review was conducted using peer-reviewed literature indexed across PubMed, Scopus, Web of Science, and IEEE Xplore. The review followed a structured evidence-mapping approach based on population, concept, and context criteria for pharmaceutical manufacturing digital twins. The evidence base is concentrated in continuous solid dosage manufacturing, biopharmaceutical processing, and selected model-based control environments. Mechanistic and hybrid models dominate the literature, while end-to-end PAT-coupled validation and prospective real-time release applications remain limited. Digital twin research in pharmaceutical manufacturing is growing but remains largely proof-of-concept. Significant work is needed to establish regulatory-grade validation, lifecycle model management, and GMP-compatible evidence standards.

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Introduction

The pharmaceutical industry's movement toward advanced manufacturing has created a need for predictive, real-time control strategies that can connect process understanding with quality assurance. Continuous manufacturing studies have shown how flowsheet modeling, risk assessment, and control frameworks can support more adaptive drug product production [1, 2], while model predictive control has been explored for integrated continuous manufacturing platforms [3]. In this setting, digital twins are increasingly positioned as an extension of Quality by Design rather than as a purely computational innovation [4]. The evidence base therefore spans manufacturing science, process systems engineering, analytical chemistry, and regulatory quality systems.

The concept of the digital twin refers to a dynamic virtual representation of a physical product, unit operation, or process that is updated through data exchange with the real system. General manufacturing reviews have characterized digital twins as part of a wider shift toward cyber-physical production systems [5], while broader systematic reviews have emphasized simulation, synchronization, lifecycle representation, and decision support as recurring features. The digital twin paradigm has also been generalized across engineering domains as a decision-support construct that connects physical assets, virtual models, and data streams. These origins explain why pharmaceutical applications have borrowed heavily from manufacturing engineering while adapting the concept to stricter quality and regulatory expectations.

Pharmaceutical digital twins face distinct challenges because the modeled system is not only a production asset but also part of a regulated quality-control environment. Material variability, powder flow behavior, bioprocess complexity, and analytical measurement uncertainty complicate model development, especially when models are expected to support quality predictions or release decisions [6, 7]. In biopharmaceutical manufacturing, the challenge is intensified by biological variability and

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process sensitivity, which has motivated work on dynamic metabolic models and biologics-specific digital twins [8, 9]. These characteristics make validation, lifecycle maintenance, and fit-for-purpose qualification central to any GMP-relevant digital twin architecture.

A scoping review is appropriate because the literature on pharmaceutical manufacturing digital twins is heterogeneous, rapidly emerging, and unevenly distributed across technologies and process domains. Existing reviews have described digital twins broadly in pharmaceutical and biopharmaceutical manufacturing [10] and have more recently framed their relevance from drug discovery through continuous manufacturing [11]. However, the evidence base still requires structured mapping across process modeling, PAT integration, validation, real-time release testing, and regulatory implementation. This review therefore maps what has been studied, where evidence is concentrated, and which dimensions remain underdeveloped.

Materials and Methods

Scoping Review Framework

This review followed a scoping review logic designed to map evidence rather than estimate pooled effects or generate performance claims. The approach was suitable because the included literature ranges from general digital twin classifications [5] to pharmaceutical manufacturing architectures [10, 11], process simulations [1, 2], PAT-enabled systems [7, 12], and bioprocess-specific digital twins [8, 9]. The review questions were framed around the population of pharmaceutical manufacturing processes, the concept of digital twins, and the context of development, control, validation, and quality assurance. This structure allowed the synthesis to remain descriptive while preserving distinctions among conceptual frameworks, computational models, and implemented manufacturing applications.

Search Strategy

The search strategy targeted peer-reviewed publications from 1 January 2017 to 31 December 2026 across PubMed, Scopus, Web of Science, and IEEE Xplore. Search terms combined "digital twin" with pharmaceutical manufacturing, Process Analytical Technology, real-time release testing, hybrid modeling, continuous manufacturing, Quality by Design, and process modeling, reflecting terminology used in pharmaceutical digital twin reviews and applications [4, 10, 12]. Additional targeted searching was used for continuous solid dosage manufacturing [6, 13], biomanufacturing and biologics [8, 9, 14], and model-based pharmaceutical control [3, 15, 16]. The strategy was designed to capture literature that explicitly used digital twin terminology as well as adjacent work that provides technical foundations for digital twin implementation.

Inclusion and Exclusion Criteria

Studies were eligible if they addressed pharmaceutical or biopharmaceutical manufacturing processes and included digital twin frameworks, enabling process models, PAT-linked architectures, validation strategies, or model-informed quality-control applications. The included evidence therefore covered solid dosage forms, continuous direct compression, lyophilization, cell culture, virus-like particle production, adjuvant manufacturing, and integrated continuous processing [6, 8, 13, 14, 17]. Studies focused only on non-pharmaceutical manufacturing were excluded unless they provided a transferable digital twin classification or implementation framework relevant to pharmaceutical manufacturing interpretation [5]. Grey literature, non-English papers, non-peer-reviewed materials, and studies outside the 2017–2026 window were excluded to maintain a reproducible peer-reviewed evidence base.

Screening and Selection

A two-stage screening process was used, first at title and abstract level and then at full-text level. Records were judged against the review focus on digital twins, process modeling, PAT integration, validation, RTRT relevance, and pharmaceutical manufacturing context, with particular attention to whether papers addressed manufacturing processes rather than only discovery or clinical applications [10, 11]. During full-text screening, studies that used model-based continuous manufacturing methods without explicit digital twin terminology were retained only when they contributed directly to the technical architecture of pharmaceutical digital twins, such as flowsheet modeling, residence time distribution modeling, or model predictive control [1, 16, 18]. This approach allowed the final map to include both explicit digital twin papers and foundational enabling studies.

Data Charting

Data were charted using a structured extraction form that captured manufacturing domain, unit operation, modeling approach, PAT or sensor integration, validation method, regulatory context, and decision-use application. Modeling categories included mechanistic, data-driven, and hybrid approaches, reflecting distinctions discussed in pharmaceutical process modeling and digital twin literature [19, 20]. PAT-related extraction captured whether NIR, Raman, FBRM, or other process measurements were described as monitoring inputs, model-updating signals, or control-system components [7, 12]. Validation extraction distinguished statistical comparison, independent experimental confirmation, uncertainty treatment, plant-model mismatch handling, and regulatory decision readiness [15, 21].

Synthesis and Presentation

The synthesis combined descriptive numerical mapping with thematic narrative interpretation. Publications were grouped by manufacturing process, model architecture, PAT coupling, validation depth, regulatory orientation, and RTRT relevance, following the evidence-mapping purpose of a scoping review rather than a meta-analysis. General digital twin reviews were used to position terminology and conceptual boundaries [5], while pharmaceutical-specific studies were used to map implementation patterns in drug product and biopharmaceutical manufacturing [4, 10, 11]. The results are presented as an evidence landscape, emphasizing concentrations, absences, and cross-cutting implementation challenges.

Results and Discussion

Search Results and Study Selection

The search identified 1,462 records across PubMed, Scopus, Web of Science, and IEEE Xplore, with an additional 42 records identified through citation tracking of pharmaceutical digital twin and continuous manufacturing papers. After removal of 331 duplicates, 1,173 records underwent title and abstract screening, and 1,076 were excluded for being outside pharmaceutical manufacturing, not peer reviewed, or unrelated to digital twin-enabling process modeling. Ninety-seven full-text records were assessed, and 66 were excluded because they lacked manufacturing relevance, did not address process modeling or PAT integration, or focused only on broad Industry 4.0 concepts without pharmaceutical specificity. Thirty-one studies were included in the final evidence map, spanning explicit pharmaceutical digital twin reviews [10, 11], digital twin implementations [8, 9, 14, 17], and enabling process-control or validation studies [3, 15, 18].

Publication Trends and Geographic Distribution

The evidence base expanded gradually from 2017 onward, with early work emphasizing continuous manufacturing control and flowsheet modeling before explicit digital twin terminology became more prominent. Studies from 2017 to 2019 focused heavily on integrated continuous manufacturing, model predictive control, risk assessment, and the Quality by Design logic that later supported digital twin framing [1-3]. From 2020 onward, pharmaceutical and biopharmaceutical digital twin publications increased, including literature reviews, lyophilization models, biologics models, and PAT-enabled biomanufacturing frameworks [10, 12, 14]. The geographic and institutional distribution was dominated by academic and academic-industry research groups, with fewer papers reporting commercial-scale industrial implementation.

Manufacturing Processes and Unit Operations

The mapped literature was concentrated in continuous solid dosage manufacturing, especially direct compression, blending, tablet press control, and integrated flowsheet modeling. Digital twins for low-dose continuous powder blending and direct compression lines illustrate how residence time distribution, neural networks, and hybrid flowsheets have been used to represent drug product processes [6, 13]. Biopharmaceutical studies addressed lyophilization, antibody manufacturing, HEK293-based virus-like particle production, and adjuvant manufacturing, showing that digital twin concepts extend beyond solid oral dosage forms [8, 9, 14, 17]. However, aseptic processing, sterile fill-finish, and multi-product facility digital twins were minimally represented in the included evidence.

Table 1 shows the distribution of digital twin applications across pharmaceutical manufacturing domains, highlighting strong concentration in continuous solid oral dosage systems, moderate expansion into biopharmaceutical processes, and a clear underrepresentation of aseptic, sterile fill-finish, and multi-product facility digital twins.

Table 1. Application areas and coverage of digital twin approaches in pharmaceutical manufacturing

Manufacturing domain	Key processes	Digital twin / modeling approaches	Representative applications	Observed coverage / gap
Continuous solid oral dosage manufacturing	Direct compression, powder blending, tablet pressing	Residence time distribution (RTD) modeling, neural networks, hybrid flowsheet simulation	Low-dose continuous blending lines, integrated tablet press control systems	Highly concentrated literature base
Integrated process systems	End-to-end continuous manufacturing flowsheets	Hybrid mechanistic–data-driven digital twins	Full-line process modeling from blending to compression	Strong representation but mostly solid dosage focus
Biopharmaceutical manufacturing	Cell culture, protein production, viral vector systems	Process simulation, data-driven bioprocess models, hybrid bioreactor twins	Antibody production, HEK293 virus-like particle (VLP) manufacturing	Moderate representation, expanding scope
Lyophilization processes	Freeze-drying cycles, thermal and mass transfer control	Mechanistic thermal models, process monitoring twins	Lyophilized biologics stability and cycle optimization	Emerging but limited studies
Aseptic and sterile manufacturing	Fill-finish, contamination	Limited digital twin integration; mostly process monitoring tools	Sterile filling line monitoring (rare examples)	Major underrepresentation

	control, isolator systems			
Multi-product facilities	Facility-wide scheduling, resource allocation	High-level simulation and scheduling models	Shared equipment and campaign-based manufacturing	Very limited digital twin development

Process Modeling Approaches

Mechanistic modeling was prominent in studies that sought to represent unit operations through physical or biochemical process understanding. Lyophilization digital twins used process modeling to connect freezing, drying, and product-quality considerations [14, 22], while bioprocess digital twins used dynamic metabolic models to represent cell-culture production systems [9, 23]. Data-driven and hybrid approaches were also identified, including artificial neural networks combined with residence time distribution models for continuous powder blending [6] and hybrid flowsheet modeling for continuous direct compression [13]. Across the evidence base, hybrid modeling appears especially important because it links physical interpretability with flexibility for complex, sensor-rich manufacturing environments [19, 20].

Integration with Process Analytical Technology

PAT integration was frequently described as a central enabler of pharmaceutical digital twins, but the depth of coupling varied widely. PAT was framed as a key enabler for continuous biomanufacturing digital twins because real-time analytical signals can support monitoring, model updating, and adaptive control [12]. Reviews of PAT tools for pharmaceutical unit operations emphasized NIR, Raman spectroscopy, and related analytical technologies as foundations for continuous process verification and real-time release testing [7]. Nevertheless, many studies described the conceptual value of PAT-to-model data flow without demonstrating fully validated, closed-loop synchronization between sensors, models, process equipment, and quality decisions.

Validation and Verification Strategies

Validation approaches in the included literature ranged from model comparison against experimental data to independent test runs, plant-model mismatch assessment, and limited uncertainty treatment. Model predictive control studies addressed mismatch between the physical plant and process model, illustrating one practical validation concern for control-oriented digital twins [15]. Residence time distribution models were used to support control strategies in continuous manufacturing, showing how dynamic material tracking can contribute to process verification [18]. However, few studies translated validation into a GMP decision framework that explicitly defined model acceptance criteria, lifecycle requalification triggers, and the evidentiary threshold for release-related use.

Applications in Real-Time Release Testing

Real-time release testing appeared more often as an intended application or quality-assurance vision than as a prospectively validated digital twin outcome. PAT literature links real-time measurement, continuous process verification, and RTRT as part of a model-informed control strategy [7], while pharmaceutical continuous manufacturing studies show how flowsheet models and control systems can support quality prediction [1, 3]. Digital twin papers for drug product manufacturing and Pharma 4.0 nanosuspension workflows suggest that model-informed quality predictions could eventually support release-relevant decisions [13, 24]. Yet direct evidence of digital-twin-driven RTRT in GMP production remains limited, and most work remains simulation-based or pilot-scale.

Regulatory and GMP Context

Regulatory and GMP considerations were present but unevenly developed across the included literature. The audit of pharmaceutical continuous manufacturing regulatory submissions highlighted that model-based approaches are increasingly relevant to submissions, although digital twin qualification as a regulatory category remains immature [21]. Digital twin and QbD-oriented biologics work explicitly raised whether approval under QbD and PAT approaches is acceptable without digital-twin-level modeling and process understanding [4]. Across the mapped evidence, regulatory discussion most often appeared as contextual justification rather than as a detailed framework for model qualification, data governance, audit trails, or lifecycle maintenance.

Table 2 shows the uneven development of regulatory and GMP considerations in digital twin–enabled pharmaceutical manufacturing, with most studies emphasizing conceptual alignment to QbD and PAT rather than providing structured frameworks for model qualification, data governance, and lifecycle regulatory control.

Table 2. Regulatory and GMP considerations in digital twin–enabled pharmaceutical manufacturing

Regulatory aspect	Current status in literature	Key emphasis	Identified gap
Model-based submissions in continuous manufacturing	Increasingly referenced in regulatory submissions for advanced manufacturing	Use of mechanistic, statistical, and hybrid models to support filings	Lack of standardized qualification criteria for digital twin models

Digital twin qualification	Emerging but not formally defined as a regulatory category	Conceptual discussion of digital twin readiness and validation	No harmonized regulatory framework for "digital twin qualification"
QbD and PAT alignment	Frequently discussed in biologics and continuous manufacturing	Use of Quality by Design (QbD) and Process Analytical Technology (PAT) principles	Unclear whether QbD/PAT alone is sufficient without full digital twin integration
Regulatory framing in studies	Mostly contextual rather than procedural	Used to justify technological relevance	Limited operational detail on compliance pathways
Model governance and lifecycle management	Rarely detailed	General mention of validation and model use in process control	Insufficient guidance on lifecycle updates, drift management, and revalidation
Data governance and auditability	Underrepresented	Occasional reference to data integrity requirements	Weak focus on traceability, audit trails, and regulatory-grade data pipelines

Evidence Gaps Identified in the Literature

The included studies repeatedly point toward gaps in scale-up, integration, validation, data infrastructure, and workforce readiness. General digital twin reviews emphasize that implementation requires not only modeling but also reliable data exchange, synchronization, lifecycle representation, and decision integration. Pharmaceutical studies similarly show that many examples remain unit-operation specific, with limited evidence for plant-wide digital twins or commercial lifecycle deployment [10, 11]. The gap is therefore not simply the absence of models but the absence of validated, maintained, GMP-compatible digital twin ecosystems that connect models, PAT, equipment, operators, quality systems, and regulatory decision-making.

Table 3 organizes the mapped literature into an evidence-maturity matrix that distinguishes current technical demonstrations from the evidence needed for GMP-relevant digital twin implementation.

Table 3. Evidence-maturity matrix for pharmaceutical manufacturing digital twins across modeling, PAT coupling, validation, and GMP decision use

Evidence-maturity dimension	What the current literature demonstrates	What remains weak or underdeveloped	Why this matters for pharmaceutical manufacturing	Minimum evidence needed for GMP-relevant progression
Manufacturing scope	Evidence is concentrated in continuous solid dosage manufacturing, direct compression, powder blending, tablet press control, lyophilization, cell culture, virus-like particle production, and selected adjuvant workflows.	Plant-wide, multi-product, sterile fill-finish, aseptic processing, packaging, and lifecycle manufacturing twins are minimally represented.	A digital twin that models only one unit operation may support development learning but cannot yet guide whole-process quality assurance.	Demonstration across linked unit operations, material transfer points, process histories, and quality decision nodes.
Model architecture	Mechanistic, data-driven, and hybrid models are all represented, with hybrid models emerging as the most translationally promising architecture.	Model boundaries, assumptions, parameter drift, data-dependence, and interpretability are inconsistently reported.	Pharmaceutical decision-makers require models that are both predictive and scientifically explainable under variable manufacturing conditions.	Explicit description of model structure, assumptions, uncertainty, intended use, data sources, retraining logic, and interpretability method.
PAT and sensor integration	PAT is repeatedly described as a central enabler, especially through NIR, Raman, FBRM, process sensors, and real-time analytical data streams.	Many studies do not validate PAT, preprocessing, model updating, equipment response, and quality decision logic as one coupled system.	A digital twin cannot support real-time quality assurance if the analytical signal and model output are not jointly reliable.	End-to-end validation of sensor performance, preprocessing stability, model updating, control linkage, and quality-prediction robustness.
Validation depth	Some studies report experimental comparison, independent confirmation, residence time distribution analysis, model predictive control testing, and plant–model mismatch evaluation.	Few studies define regulatory-grade acceptance criteria, requalification triggers, model risk classification, or lifecycle verification procedures.	Validation determines whether a twin is a development model, a decision-support tool, or a release-relevant quality system.	Fit-for-purpose validation plan with predefined acceptance thresholds, uncertainty bounds, stress testing, change-control rules, and human review points.
Regulatory and GMP positioning	Regulatory relevance is frequently acknowledged	Digital twin qualification is rarely translated into	GMP use requires not only technical accuracy	Governance framework covering intended use,

	through Quality by Design, PAT, continuous manufacturing, and model-based control discussions.	data integrity, audit trail, cybersecurity, model governance, or submission-ready evidence requirements.	but also traceability, accountability, and documented control of model-supported decisions.	auditability, data lineage, access control, change management, model monitoring, and deviation handling.
RTRT readiness	RTRT is a recurring aspirational application because digital twins align with real-time process understanding and model-informed quality prediction.	Prospective evidence of digital-twin-driven RTRT in routine GMP production remains limited.	Release-relevant use carries the highest evidentiary burden because predicted quality attributes may influence batch disposition.	Prospective demonstration that predicted critical quality attributes remain reliable under routine process variability and are acceptable within a regulated control strategy.
Lifecycle management	General digital twin theory emphasizes synchronization, lifecycle representation, and decision integration.	Pharmaceutical examples rarely show maintained twins across development, scale-up, commercial production, deviation management, and post-approval change.	A static model cannot remain trustworthy when materials, equipment, process conditions, products, or control strategies change.	Defined lifecycle plan for model monitoring, drift detection, revalidation, documentation updates, and post-change performance confirmation.
Human oversight and organizational integration	The literature recognizes that digital twins support decision-making rather than replacing manufacturing, quality, and regulatory expertise.	Few studies specify how operators, process engineers, quality teams, and regulators should interact with model outputs.	Human interpretation is essential when model predictions influence process adjustments, deviation prevention, or release-related judgments.	Role-specific decision workflow showing who reviews outputs, when escalation occurs, and how model evidence is documented in the quality system.

The Current Landscape is Proof-of-Concept Dominated

The current evidence base is best characterized as proof-of-concept dominated, with most studies demonstrating feasibility in a single unit operation, model class, or controlled pilot environment. Solid dosage examples include blending, direct compression, and tablet press control [6, 13, 15], while biopharmaceutical examples include lyophilization, antibody manufacturing, and virus-like particle production [8, 9, 14]. These studies are valuable because they define technical possibilities, but they do not yet constitute a mature evidence base for end-to-end pharmaceutical digital twins. Plant-wide architectures spanning material receipt, processing, testing, release, and lifecycle maintenance remain conspicuously absent.

Hybrid Models Bridge Mechanistic Understanding and Data

Hybrid models appear especially well suited to pharmaceutical manufacturing because they combine mechanistic process knowledge with the adaptability of data-driven learning. The included literature shows this pattern in hybrid flowsheet modeling for continuous direct compression [13], neural network and residence time distribution combinations for continuous blending [6], and broader discussions of hybrid modeling strategies in continuous pharmaceutical manufacturing [19]. Mechanistic, data-driven, and hybrid approaches each contribute different strengths, but hybrid models may best address the dual requirement for predictive performance and scientific interpretability [20]. This explains why hybrid architectures are frequently proposed as a bridge between pharmaceutical process understanding and digital twin flexibility.

PAT Integration is Described but Not Validated as a Coupled System

PAT integration is one of the most frequently cited enablers of pharmaceutical digital twins, yet the evidence rarely validates the sensor-model-control system as a coupled whole. Continuous biomanufacturing work describes PAT as a key enabler for digital twins because it provides real-time data streams for process monitoring and model updating [12]. Reviews of PAT in pharmaceutical unit operations similarly frame NIR, Raman, and related tools as foundations for continuous verification and RTRT [7]. However, the literature generally stops short of demonstrating that the analytical method, preprocessing pipeline, model, control logic, and quality decision function remain jointly validated over time.

Validation Frameworks are the Critical Missing Link

Validation is the critical missing link between digital twin feasibility and GMP-relevant implementation. Several studies validate models statistically or experimentally, such as through model predictive control mismatch evaluation [15], residence time distribution-based control strategy development [18], or process simulation and risk assessment [2]. These approaches are important, but they do not fully resolve how a digital twin should be qualified when it supports regulated decisions such as process adjustment, deviation prevention, or release testing. A regulatory-grade framework would need to define intended use, model boundaries, uncertainty acceptance, change control, data integrity, and lifecycle verification.

Figure 1 illustrates the evidence-to-implementation architecture through which pharmaceutical manufacturing digital twins move from unit-operation models and PAT-linked prototypes toward validated, GMP-compatible, and release-relevant decision systems.

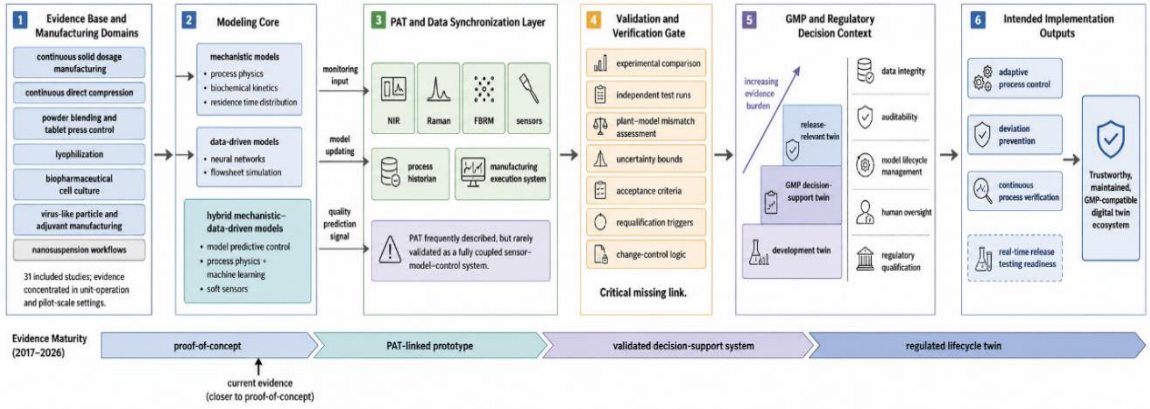

Figure 1. Evidence-to-implementation architecture for digital twins in pharmaceutical manufacturing.

The Journey from Digital Twin to RTRT Remains Aspirational

The conceptual alignment between digital twins and RTRT is strong because both depend on real-time process understanding, validated models, and confidence that quality can be assured without relying solely on end-product testing. Continuous manufacturing control studies show how predictive control and flowsheet modeling can move quality assurance closer to the process itself [1, 3], while PAT literature explicitly links process monitoring to real-time release testing [7]. Digital twin applications in nanosuspension processing and continuous direct compression further suggest that model-informed release may become feasible in specific contexts [13, 24]. At present, however, the mapped literature provides limited prospective evidence that digital twins have been accepted or routinely used as RTRT decision engines in GMP production.

Limitations

Scoping Review Limitations

This scoping review was limited to English-language, peer-reviewed publications from 2017 to 2026, which may have excluded relevant technical reports, proprietary case studies, and regulatory interactions not available in the public literature. Because digital twin implementation is commercially sensitive, industry-internal developments in data architecture, model maintenance, PAT integration, and validation may be underrepresented relative to academic publications [11, 21]. The review also included some foundational continuous manufacturing and digital twin classification studies that did not always use pharmaceutical digital twin terminology explicitly, but these were retained when they informed modeling, control, or implementation concepts [1, 5]. As a result, the map should be interpreted as a structured view of the accessible peer-reviewed evidence rather than a complete account of all industrial practice.

Mapped Literature Limitations

The mapped literature itself has important limitations, including inconsistent definitions of "digital twin," heterogeneous model reporting, and limited standardization of validation evidence. General digital twin reviews show that terminology varies across simulation models, synchronized cyber-physical systems, and lifecycle decision platforms, while pharmaceutical studies often apply the term to unit-operation models rather than fully synchronized manufacturing twins [10, 13, 14]. Many studies remain simulation-based, pilot-scale, or narrowly focused on individual process components, which limits inference about GMP scalability and lifecycle robustness. These limitations underscore the need for clearer reporting standards and regulatory-grade validation methods before digital twins can become routine elements of pharmaceutical control strategies.

Recommendations

For Researchers

Researchers should standardize how pharmaceutical digital twins are defined, classified, and reported so that future studies can be compared across process types and modeling approaches. Current literature uses digital twin terminology across a spectrum that includes flowsheet models, synchronized process simulations, PAT-linked control systems, and lifecycle decision-support platforms [5, 10]. Future studies should explicitly state whether the digital twin is descriptive, predictive, prescriptive, adaptive, or lifecycle-maintained, because these categories imply different validation burdens and regulatory uses. Transparent reporting of model structure, assumptions, data sources, uncertainty handling, and maintenance plans would strengthen the scientific value of digital twin studies and reduce ambiguity across the field.

For Industry and Technology Developers

Industry and technology developers should invest in scalable data infrastructure that enables synchronization between process equipment, PAT sensors, manufacturing execution systems, quality systems, and model environments. The evidence suggests that digital twins require more than isolated models; they depend on reliable real-time data exchange, contextualized process histories, and validated interfaces between analytical measurements and predictive algorithms [7, 12, 25]. Continuous manufacturing and bioprocessing examples show that meaningful implementation requires integration across unit operations, control systems, and quality decision points rather than stand-alone simulation tools [8, 13, 17]. Developers should therefore prioritize interoperability, auditability, cybersecurity, data integrity, and lifecycle model governance as core technical requirements.

For Regulators

Regulators should collaborate with academia and industry to develop guidance on digital twin qualification, lifecycle maintenance, and the evidentiary role of digital twins in control strategies and RTRT submissions. Existing continuous manufacturing regulatory experience shows that model-based approaches are increasingly relevant to submissions, but the specific qualification expectations for digital twins remain underdeveloped [21]. QbD and PAT-oriented literature indicates that digital twins could support deeper process understanding, but only if their intended use, validation status, uncertainty limits, and change-control procedures are clearly defined [4, 7]. A collaborative regulatory framework could help distinguish exploratory development twins from GMP decision-support twins and release-relevant digital twins.

Table 4 proposes a decision-use qualification framework that clarifies how validation and governance requirements escalate as digital twins move from development tools toward GMP decision support and real-time release testing.

Table 4. Decision-use qualification framework for translating pharmaceutical digital twins from development models to release-relevant quality systems

Digital twin decision-use tier	Primary purpose	Typical evidence status in the reviewed literature	Validation burden	Governance requirements	Example pharmaceutical use case	Risk if inadequately qualified
Tier 1: Exploratory development twin	Supports process understanding, hypothesis generation, design-space exploration, and early process simulation.	Strongest representation in the literature, especially in unit-operation simulations, flowsheet models, and bioprocess modeling.	Basic scientific plausibility, comparison with development data, transparent assumptions, and documentation of model boundaries.	Research documentation, version control, and clear separation from GMP decision-making.	Simulating drying behavior in lyophilization or exploring powder-blending dynamics before process optimization.	Overinterpretation of development simulations as validated control evidence.
Tier 2: Engineering optimization twin	Supports process optimization, scale-up planning, troubleshooting, and sensitivity assessment.	Moderately represented through continuous manufacturing, process-control, and risk-assessment studies.	Independent experimental comparison, stress testing across operating ranges, sensitivity analysis, and parameter uncertainty assessment.	Engineering change documentation, model-version traceability, and review by process-development teams.	Evaluating residence time distribution behavior during continuous direct compression scale-up.	Process changes may be guided by models that do not generalize across materials, equipment, or operating conditions.
Tier 3: PAT-linked monitoring twin	Uses real-time analytical or process data to update process-state estimates and detect deviations.	Conceptually common, but fully validated PAT-to-model synchronization is limited.	Joint validation of sensor performance, preprocessing, model updating, sampling frequency, measurement uncertainty, and process-state estimation.	Data integrity controls, audit trails, instrument calibration linkage, and defined response procedures for abnormal model outputs.	Using NIR or Raman signals to update a model of blend uniformity or intermediate product quality.	False confidence in real-time monitoring if analytical drift, preprocessing errors, or model mismatch are not controlled.

Tier 4: Control-support twin	Provides recommendations or automated support for adaptive control, process adjustment, or deviation prevention.	Emerging but less mature; represented mainly through model predictive control and continuous manufacturing studies.	Closed-loop or semi-closed-loop testing, plant–model mismatch evaluation, fail-safe analysis, human override logic, and control-action verification.	Change-control linkage, operator training, escalation rules, cybersecurity protection, and documented accountability for actions.	Supporting tablet press adjustment, continuous line control, or bioprocess set-point optimization.	Inappropriate control actions may introduce quality drift, process instability, or undocumented deviations.
Tier 5: GMP decision-support twin	Produces model outputs that influence quality decisions but do not independently determine release.	Rarely demonstrated as a mature implementation; mostly discussed as a future direction.	Predefined intended use, acceptance criteria, uncertainty thresholds, ongoing performance monitoring, and periodic requalification.	Quality-system ownership, validation master plan integration, auditability, role-based access, deviation documentation, and lifecycle governance.	Providing quality teams with model-informed evidence during deviation investigation or continuous process verification.	Quality decisions may rely on poorly bounded predictions without sufficient traceability or review.
Tier 6: Release-relevant RTRT twin	Supports or contributes directly to real-time release testing and batch disposition decisions.	Largely aspirational in the mapped literature; direct prospective GMP evidence remains limited.	Highest burden: prospective validation under routine variability, equivalence to or replacement logic for end-product testing, robust uncertainty handling, regulatory acceptance, and lifecycle revalidation.	Formal regulatory strategy, submission-ready documentation, validated data pipelines, model-risk management, batch-level audit trails, and mandatory expert oversight.	Predicting assay, content uniformity, dissolution, or critical intermediate quality attributes for release-relevant decisions.	Invalid release decisions, patient-risk exposure, regulatory non-compliance, and loss of confidence in model-informed quality systems.

Research Gaps

End-to-End and Lifecycle Digital Twins

A major research gap is the absence of end-to-end pharmaceutical digital twins that span multiple unit operations and remain maintained across the product lifecycle. Current examples are concentrated in individual or narrowly bounded processes, including blending, direct compression, lyophilization, cell culture, virus-like particle production, and adjuvant manufacturing [6, 8, 13, 14, 17]. Although integrated continuous manufacturing studies demonstrate important foundations for plant-level modeling and control [1, 3], the evidence does not yet show a fully synchronized lifecycle twin connecting development, scale-up, commercial manufacturing, deviation handling, and post-approval change management. Future research should therefore examine how digital twins evolve as products, processes, equipment, materials, and control strategies change over time.

Regulatory-Grade Validation Methodology

A second major gap is the lack of consensus methodology for demonstrating that a pharmaceutical digital twin is fit for a defined GMP decision. Existing validation approaches include statistical model testing, residence time distribution confirmation, plant-model mismatch analysis, and process simulation assessment [2, 15, 18]. These methods are necessary but insufficient when a digital twin is expected to support regulated actions such as adaptive control, batch disposition, deviation prevention, or RTRT [7, 21]. A regulatory-grade methodology should specify the relationship between model risk, intended use, data quality, uncertainty bounds, monitoring frequency, revalidation triggers, and human oversight.

Implications

For Pharmaceutical Manufacturing Advancement

Digital twins could transform pharmaceutical manufacturing by making process development, scale-up, troubleshooting, and control more predictive and scientifically grounded. The evidence base shows that mechanistic models, hybrid architectures, and model predictive control can represent important aspects of continuous manufacturing and bioprocessing [3, 9, 13, 20]. If integrated effectively, these approaches could reduce reliance on trial-and-error process adjustment and support more proactive

quality assurance. However, the transformative potential of digital twins depends on whether validation, data infrastructure, and lifecycle governance mature at the same pace as modeling innovation.

For Quality Assurance and Release Testing

For quality assurance, digital twins imply a shift from retrospective batch testing toward continuous, model-informed assurance of process and product quality. PAT-enabled monitoring, continuous process verification, and model-based quality prediction are already aligned with this direction [7, 12, 18]. However, RTRT supported by digital twins requires stronger evidence that predicted quality attributes such as assay, content uniformity, dissolution, or process-critical intermediates are reliable under routine manufacturing variability [6, 13, 24]. This shift would require not only technical validation but also cultural change in how manufacturing, quality, engineering, and regulatory teams interpret model-supported evidence.

For the Research-Industry-Regulatory Interface

The emergence of pharmaceutical digital twins creates a shared evidence-building challenge for researchers, industry developers, and regulators. Researchers can define model architectures and validation science, industry can test implementation under realistic GMP constraints, and regulators can clarify how digital twin evidence should be evaluated within control strategies [4, 11, 21]. General digital twin literature emphasizes that the paradigm depends on sustained synchronization and decision integration rather than static simulation alone. A tripartite collaboration is therefore essential to move the field from fragmented demonstrations toward trustworthy, qualified, and lifecycle-managed digital twin systems.

Conclusion

Digital twin research in pharmaceutical manufacturing is growing rapidly but remains early-stage. The evidence is concentrated on isolated unit operations, particularly in continuous solid dosage form manufacturing and selected biopharmaceutical processes.

Hybrid mechanistic-data-driven models integrated with PAT sensors represent the predominant architectural paradigm. However, the evidence for routine operational use in GMP manufacturing environments remains limited.

The most significant barrier to realizing the digital twin vision is the absence of validated and regulatorily accepted frameworks for model qualification, lifecycle management, and RTRT decision-making. Without such frameworks, digital twins are likely to remain valuable development and simulation tools rather than release-relevant quality systems.

A concerted multi-stakeholder effort is needed to close validation, integration, and governance gaps. The future role of digital twins in pharmaceutical manufacturing will depend on whether the field can translate modeling sophistication into trustworthy quality assurance and regulated decision support.

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