



Digital Twins as Enabler of Resilience in Pharmaceutical Supply Chains: Technological Applications, AI Implementation Gaps, and Regulatory Decision-Making

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ABSTRACT

Recent disruptions, including the COVID-19 pandemic, geopolitical instability, and demand fluctuations, have exposed vulnerabilities in pharmaceutical supply chains and increased the need for resilient and adaptive systems. Digital Twins (DTs), integrating Internet of Things (IoT) technologies, artificial intelligence, real-time data, and simulation, offer opportunities to improve supply chain visibility, prediction, decision-making, and resilience. However, existing research on DT applications in pharmaceutical supply chains remains fragmented, with limited synthesis of regulatory and policy perspectives. This study conducts a Systematic Literature Review (SLR), following the PRISMA framework, to examine the applications, benefits, evaluation approaches, and research gaps associated with DTs in pharmaceutical supply chain resilience. Searches of Scopus, Web of Science, and Google Scholar identified 18 core studies for analysis. In addition, 13 international policy and regulatory documents were reviewed to examine the alignment between academic research and regulatory priorities. The findings identify six major application areas: manufacturing and production, inventory management, logistics and distribution, cold chain management, quality management, and end-to-end supply chain management. DTs contribute to enhanced visibility, forecasting, adaptability, resilience, and regulatory compliance. However, current research relies predominantly on scenario simulation, mathematical optimization, and conceptual frameworks, with limited empirical and real-world validation. Three major research gaps are identified: insufficient attention to organizational and human factors, immature cross-organizational data-sharing and collaboration mechanisms, and limited research on regulatory governance and implementation. Policy documents additionally emphasize model validation, data governance, cybersecurity, and compliance. Future research should therefore integrate technological innovation with organizational, data, and governance mechanisms to support resilient and practically deployable pharmaceutical supply chains.

1. Introduction

1.1 Research Background

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In recent years, major global disruptions such as the COVID-19 pandemic, demand shocks, and lead time extensions (e.g., transportation delays) have significantly increased supply chain uncertainty, underscoring the critical need for supply chain resilience [1]. In this highly uncertain environment, the pharmaceutical supply chain faces higher risks than the general manufacturing industry because its stable operation directly impacts patient survival and public health. As these products are among the most life-saving drugs, they are subject to strict time constraints, and any delays in production or delivery can lead to serious medical consequences. Furthermore, the extensive dependence on cold chain logistics increases the vulnerability of the pharmaceutical sector, making temperature-sensitive products like biologics and vaccines extremely susceptible to disruptions during transportation and storage [2]. Compared to other industries, the pharmaceutical supply chain is also under stricter regulatory supervision with rigorous requirements for quality management. However, traditional pharmaceutical supply chain management remains overly dependent on a passive, fragmented operational mode, making it increasingly difficult to meet these complex cold chain requirements and stringent regulatory standards [3-4]. This passive structure lacks the operational agility needed to rapidly re-route supplies during sudden lead-time delays, as well as the systemic resilience required to absorb disruption shocks without escalating into critical drug shortages. Therefore, building dynamic resilience and proactive agility into the pharmaceutical supply chain has become a paramount operational priority.

The origins of the Digital Twins (DT) concept can be traced back to the NASA Apollo program in the 1960s. In modern supply chain management, a DT is defined as a dynamic, real-time virtual representation of a physical system that integrates Internet of Things (IoT) data, sensors, and simulation models [2]. Its core characteristics include continuous data synchronization, real-time visibility, and the ability to conduct risk-free "what-if" scenario analyses [1,5,6]. DT is exceptionally well-suited for pharmaceutical supply chains because of the industry's strict time constraints and the high value of life-saving products. By utilizing DT, pharmaceutical companies can simulate complex disruptions, such as demand surges or transportation delays, and test response strategies virtually before actual implementation [1,7].

The modern pharmaceutical supply chain faces several unique and pressing operational challenges that traditional management models cannot adequately resolve. First, there is a heavy reliance on the cold chain; temperature-sensitive products like biologics and vaccines are highly susceptible to spoilage during transportation, making traditional static buffer inventory extremely expensive and operationally inefficient [2]. Second, the industry operates under strict regulatory compliance constraints, such as Good Manufacturing Practice (GMP) and FDA guidelines, which demand absolute data integrity and rigorous quality control. Third, the pharmaceutical ecosystem is a complex global network spanning upstream Active Pharmaceutical Ingredient (API) manufacturers, fill-finish lines, wholesalers, and terminal hospital pharmacies. Any localized disruption, such as a single API plant shutdown, can cause a severe "ripple effect" downstream, ultimately leading to critical drug shortages that directly impact patient survival. While the integration of Industry 4.0 technologies has gained momentum, current literature regarding DT adoption in the pharmaceutical sector reveals several critical gaps. Firstly, existing studies are highly fragmented across various disciplines and often limited to general technology introductions or isolated case studies. There is a prominent lack of systematic categorization to provide a structured blueprint for DT applications. Secondly, most technical models originate from the general fast-moving consumer goods (FMCG) sector and lack a specific resilience focus tailored to the unique physical constraints and concurrent disruptions of the pharmaceutical industry [1]. Finally, there is a significant lack of policy integration. Current academic

research often focuses purely on technological capabilities, failing to address the practical regulatory barriers and operational policies required for real-world implementation.

Furthermore, while the initial Systematic Literature Review (SLR) identified highly relevant peer-reviewed articles, the rapid emergence of DT technology in the highly regulated pharmaceutical sector means that academic research often lacks practical regulatory alignment. As highlighted by recent studies, regulatory barriers and the absence of specific operational policies remain significant obstacles to the large-scale adoption of DT in healthcare and pharmaceutical supply chains [4]. To bridge this critical gap between theoretical technical architectures and real-world regulatory compliance, this research will evaluate key policy documents and regulatory guidelines across major global regions, including the UK, Europe, the Americas, Asia, and Africa. By integrating global policy perspectives, this study aims to provide a more holistic and actionable end-to-end recovery framework that aligns with stringent pharmaceutical standards, such as GMP and FDA data integrity requirements. The framework will be beneficial for examining how DT are used to improve supply chain resilience in the pharmaceutical industry.

To achieve this overarching goal, this study will explore the following core research questions (RQs):

RQ1: What are the reported DT application areas in pharmaceutical supply chain resilience?

RQ2: What resilience capabilities (e.g., visibility, resiliency, robustness, compliance, adaptability) can support DT implementation?

RQ3: How are DT applications evaluated?

RQ4: What are the current research gaps and future research opportunities?

1.2 Literature Review

1.2.1 Evolution of Pharmaceutical Supply Chain Resilience

The necessity and timeliness of this study are firmly grounded in foundational and recent supply chain management literature. Ivanov [8] emphasizes that future supply chain designs must prioritize structural resilience and adaptability, as traditional systems lack the structural flexibility to withstand and adapt to prolonged macro-level disruptions. Building on this, Pettit et al. [9] highlight the critical need for enterprises to balance "Vulnerabilities" and "Capabilities" to maintain long-term operational continuity. To operationalize these resilience frameworks, Ivanov & Dolgui [5] conceptualized the "Digital Supply Chain Twin," demonstrating its pivotal role in integrating simulation, optimization, and real-time data analytics to achieve end-to-end visibility and proactively test recovery strategies. Furthermore, recent studies [2,4] underline the urgent need to adapt these technological concepts specifically for the highly regulated and cold-chain-dependent medical sector.

Early pharma supply chain resilience was mainly built on a traditional management approach, which is normally designed for linear and predictable environments. In the pharmaceutical industry, to ensure patient safety and meet stricter regulations, the traditional strategy is highly dependent on safety inventory and purchasing API, as an emergency buffer to deal with risks. However, these methods are static and passive in nature and often respond after a supply interruption or performance decline. In addition, many life-saving drugs, such as biological agents and vaccines, have a strict shelf life and are highly dependent on cold chain logistics with temperature control, which makes maintaining a huge static buffer inventory not only expensive but also extremely inefficient and inflexible in operation [2]. In today's highly dynamic and uncertain global market, the limitations of such passive strategies have become increasingly obvious.

Historically, pharmaceutical supply chain management relied primarily on static buffer inventory and safety stock to decouple supply and demand uncertainties, aiming to ensure 100% product

availability under strict regulatory requirements. However, in the medical sector, where biopharmaceuticals, biologics, and vaccines possess high temperature sensitivity and strict shelf lives, maintaining large static buffer inventories proved operationally rigid, financially prohibitive, and highly susceptible to product spoilage [2]. These traditional strategies were inherently reactive, initiating response mechanisms only after performance degradation or severe supply delays had already occurred [3].

As global supply networks became increasingly interconnected and lean, susceptibility to systemic disruptions and downstream "ripple effects" grew significantly [5,8]. In response, supply chain literature transitioned from reactive inventory buffering toward formal supply chain risk management, defining resilience as an enterprise's capability to balance inherent structural vulnerabilities with dynamic managerial capabilities. Under the Dynamic Capability View (DCV), resilience requires continuous reconfiguration of physical, operational, and technological assets to maintain organizational continuity during environmental turbulence [10].

The unprecedented global disruptions of recent years exposed the structural boundaries of standalone forecasting models and traditional enterprise systems, driving the evolution of PSCR toward cyber-physical systems and the Viable Supply Chain (VSC) paradigm [5,8]. Modern PSCR leverages Intelligent Digital Twins (IDT) to establish continuous end-to-end visibility, perform real-time cold-chain monitoring, and conduct risk-free "what-if" stress testing in virtual environments [2,11]. By integrating predictive AI analytics with prescriptive mitigation policies such as dynamic allocation, therapeutic substitution, and selective dual sourcing, the digital-twin-enabled resilience paradigm allows pharmaceutical supply networks to proactively prevent shortages while maintaining strict compliance with Good Manufacturing Practice (GMP) and regulatory standards [11].

1.2.2 Digital Twin Capabilities in Pharma Supply Chains: Visibility and Monitoring

Within the Dynamic Capabilities View (DCV), DTs can support real-time monitoring and operational visibility in sensitive pharmaceutical supply chains, particularly in cold-chain logistics [12]. The integration of IoT and blockchain technologies can further support data integrity and enable more reliable monitoring of temperature-sensitive products [13, 14]. However, a key limitation identified in the literature is that many reported applications remain based on unidirectional data flows and therefore correspond more closely to the concept of a "Digital Shadow" than to a fully integrated DT [15]. Limited interoperability and semantic consistency across clinical, operational, and other information systems can further constrain the development of automated and closed-loop decision-making.

1.2.3 Digital Twin Capabilities in Pharma Supply Chains: Simulation and Scenario Analysis

DT provides a risk-free virtual environment, used for disruptive simulation and what-if analysis. It is based on the integration of Hybrid Modeling frameworks that integrate Discrete-Event Simulation (DES), mathematical optimization, and machine learning [1]. In the complex multi-layer pharmaceutical supply chain, researchers will use these models to test network adaptability. For instance, Spyrou et al [17] used DT with a virtual reality interface to simulate and predict weather-related route interruptions during the transportation of temperature-sensitive drugs, allowing early rerouting and preventing delivery delays. However, the current model is usually based on simplified assumptions. Because capturing all the dynamic changes and constraints in the multi-level

pharmaceutical network requires substantial computational resources, it remains difficult to integrate these models in practice [1].

1.2.4 Digital Twin Capabilities in Pharma Supply Chains: Risk Prediction

DT significantly enhance the ability to forecast demand and disruption risk by integrating big data analytics and machine learning algorithms. In the pharma industry, DTs are seen as a critical early warning system to prevent drug shortages. Other researchers have confirmed their value in this field. For example, Shah et al. [17] developed a gradient-boosted risk-scoring model in a digital split structure. By analyzing electronic health records (EHR) orders, Active Pharmaceutical Ingredient (API) production data, and logistics bottlenecks, it successfully predicted the risk of drug shortages up to 6 weeks in advance. These predictive models are based on Data-driven Risk Analytics Theory, which enables a transition from passive to active foresight control in supply chain management [11]. But the model still heavily depends on the quality of historical data; this has imposed significant restrictions on the pharmaceutical environment. Specifically, demand during an extreme situation, such as a global pandemic, is highly volatile and cannot be reliably inferred from historical data. This reduces the effectiveness of DT risk forecasting in extreme disruptions, thus limiting its contribution to resilience in terms of adaptability and robustness. This gap highlights the need for a model that can handle deep uncertainty, rather than relying solely on data-driven reasoning.

1.2.5 Digital Twin Capabilities in Pharma Supply Chains: Comparative Synthesis and Rationale

When disruptions occur, or risks are predicted, DT can provide prescriptive analysis to optimize the recovery strategy. This is theoretically supported by the Viable Supply Chain model and the Hybrid Modeling framework, which deeply integrate discrete-event simulation (DES), agent-based modeling (ABM), and mathematical optimization algorithms [1,11]. The researcher uses these hybrid models to test the complex recovery strategy in a risk-free environment in the pharmaceutical industry. For instance, policy experiments can be embedded into the digital alter ego combined with DES-ABM, automatically calculating and testing strategies such as dynamic allocation, therapeutic substitution, and selective dual procurement, and successfully reducing the expected number of drug shortage days by up to 44%. However, these models, which combine AI, simulation, and optimization calculations, have a higher initial investment cost. At present, most integration frameworks are still in the conceptual or experimental stage. To expand into a large-scale, immediate pharmaceutical environment, they still face limitations in data security, technology compatibility, and the lack of real-world empirical verification [4].

1.2.6 Digital Twin Capabilities in Pharma Supply Chains: Decision Support and Recovery

To establish the foundation and rationale of this study, recent literature in pharmaceutical Digital Twins (DT) can be synthesized into distinct operational focuses, which highlight critical opportunities for further research integration: First, there is a gap in the research context and regulatory constraints. Although Badakhshan & Ball [1] proposed an integrated hybrid simulation-optimization-machine learning framework, its application focuses primarily on general fast-moving consumer goods (FMCG). Their model is not specifically tailored to strict regulatory restrictions, like GMP, FDA data integrity requirements, and the extreme cold-chain dependence of the pharmaceutical industry. Consequently, existing frameworks struggle to ensure regulatory compliance and execution accuracy

when transferred to the medical domain. Second, there is a prominent disconnect between barrier analysis and operational strategies. Existing literature remains split into two isolated streams: diagnostic studies that map adoption hurdles, and quantitative simulation models that evaluate performance under idealized, barrier-free assumptions [4-5]. For example, Sharma et al. [4] utilized the TOE framework to systematically classify 19 adoption barriers in healthcare supply chains. While their work provides valuable diagnostic clarity, it stops short of offering prescriptive simulation models or decision-support algorithms for active disruption recovery. Similarly, Ali et al [24] reviewed AI-driven Digital Twin applications, explicitly noting a lack of integrated end-to-end disruption recovery mechanisms. As emphasized by [5, 11], offline barrier diagnostics cannot enhance resilience unless embedded into dynamic simulation-optimization frameworks that test real-time, policy-aligned recovery actions.

Second, there is a disconnect between barrier analysis and operational strategies. End-to-end disruption recovery fundamentally relies on prescriptive operational strategies, such as dynamic inventory allocation, therapeutic substitution, and selective dual sourcing, executed across multi-echelon networks during crises [1, 17]. On one hand, diagnostic studies focus exclusively on technology adoption hurdles. For example, Sharma et al. [4] utilized the TOE framework to systematically map 19 barriers (e.g., data silos, legacy system incompatibility, high deployment costs, and regulatory gaps) in healthcare supply chains. While these studies offer essential diagnostic insights into implementation obstacles, they stop short of providing actionable, prescriptive simulation models to guide operational decision-making during real-time recovery. On the other hand, operational simulation studies [17] model recovery actions assuming a barrier-free, fully integrated environment with complete data sharing. Similarly, while Shahid Ali et al. [2] reviewed AI-driven Digital Twins across healthcare domains, they highlighted that current research fails to bridge these diagnostic barriers with end-to-end operational recovery strategies. Consequently, a critical research gap exists in integrating real-world adoption barriers into prescriptive operational recovery models [5].

Finally, there is a critical gap in evaluating multi-echelon recovery models under dynamic compound disruptions. In pharmaceutical supply chain management, drug shortages represent the primary operational manifestation of supply disruptions [3, 17]. While benchmark studies have demonstrated the utility of hybrid Discrete-Event Simulation and Agent-Based Modeling (DES-ABM) Digital Twins in testing prescriptive recovery policies, such as dynamic allocation, therapeutic substitution, and selective dual sourcing, their experimental scenarios predominantly evaluate single failure modes in isolation [17]. Existing literature lacks integrated "end-to-end recovery models", defined as cyber-physical decision-support architectures that simulate and optimize multi-echelon recovery policies spanning upstream API suppliers, manufacturers, wholesalers, and terminal hospital pharmacies [5]. Such end-to-end models are essential because localized or single-node recovery strategies fail to contain the "ripple effect" caused by simultaneous dual disruptions (e.g., a drastic demand surge accompanied by an extended API lead-time delay), which represent the most severe failure scenarios during global health crises [8]. Addressing this gap directly aligns with RQ4 by identifying key future research directions to enhance systemic resilience.

2. Methodology

This study aims to systematically explore the reported DT application areas in pharmaceutical supply chain resilience, the resilience capabilities (e.g., visibility, resiliency, robustness, compliance, adaptability) that DT implementation supports, evaluate DT applications, analyze research trends,

and identify future directions. Systematic Literature Review (SLR) is used to answer research questions, as it has clear literature search strategies, inclusion and exclusion criteria, and consistent analytical procedures, effectively reducing bias caused by subjective researcher judgment and enhancing the credibility and reproducibility of research findings [18].

Additionally, to address shortcomings in the literature, specifically the disconnect between theoretical technological architectures and real-world regulatory compliance, this study incorporates relevant policy documents into the analytical framework. This methodological integration follows established precedents in management and supply chain research. For example, [18] advocates synthesizing academic literature with policy and practice evidence to develop evidence-informed management knowledge that guides real-world decision-making. In the context of digital supply chains, [19] integrated national industrial strategy policy documents with supply chain modeling to evaluate digital twins beyond theoretical hype, while [20] synthesized scholarly articles with industry and policy reports to align pharmaceutical digital twins with regulatory compliance and operational resilience. Following these approaches, this study incorporates official regulatory guidelines and policy documents from major global jurisdictions (e.g., US FDA, EMA, WHO, UK MHRA, Republic of Korea MFDS) alongside peer-reviewed literature. Through dual-perspective triangulation, this research bridges the gap between theoretical digital twin capabilities and stringent regulatory requirements (e.g., Good Manufacturing Practice (GMP) and FDA Data Integrity standards), establishing an operationally actionable end-to-end recovery framework.

2.1 Review Protocol

To ensure transparency and systematicity in the SLR process, this study followed the PRISMA 2020 guidelines for literature search and screening. PRISMA is a widely adopted international standard for systematic literature reviews, providing a consistent screening process to enhance transparency and the credibility of findings. According to PRISMA guidelines, the literature review process for this study comprises four stages: Identification, Screening, Eligibility, and Inclusion.

Identification Phase: A pre-designed search strategy across three primary databases (Scopus, WOS, and Google Scholar) yielded a total initial search pool of 344 records. Specifically, 264 records were retrieved from Scopus (representing approximately 77% of the initial literature pool), 54 records from Web of Science (WoS), and 26 records from Google Scholar. All exported records were imported into reference management software, and 2 duplicate records were removed, leaving 342 unique records for preliminary screening.

Screening Phase: The 342 unique records underwent preliminary screening based on titles, abstracts, and keywords. A total of 259 records were excluded as unrelated to the core research topic (e.g., studies lacking Digital Twin technology, non-supply chain focus, or general non-pharmaceutical manufacturing). Following this preliminary screening, 25 unretrieved articles were excluded, and 58 candidate studies ('possibly' literature) were retained for full-text qualification assessment.

Eligibility Phase: Full-text articles of the 58 candidate studies were retrieved and subjected to comprehensive evaluation against predefined inclusion and exclusion criteria. During this stage, 40 articles were excluded due to a lack of a specific supply chain resilience focus or purely clinical/patient-level medical treatment orientations.

Inclusion Phase: A total of 18 core studies (n=18) met all eligibility criteria and were finalized for structured data extraction, methodological quality assessment, and thematic synthesis.

The complete literature screening process for this study will be presented using the PRISMA Flow Diagram, as shown in Figure 1.

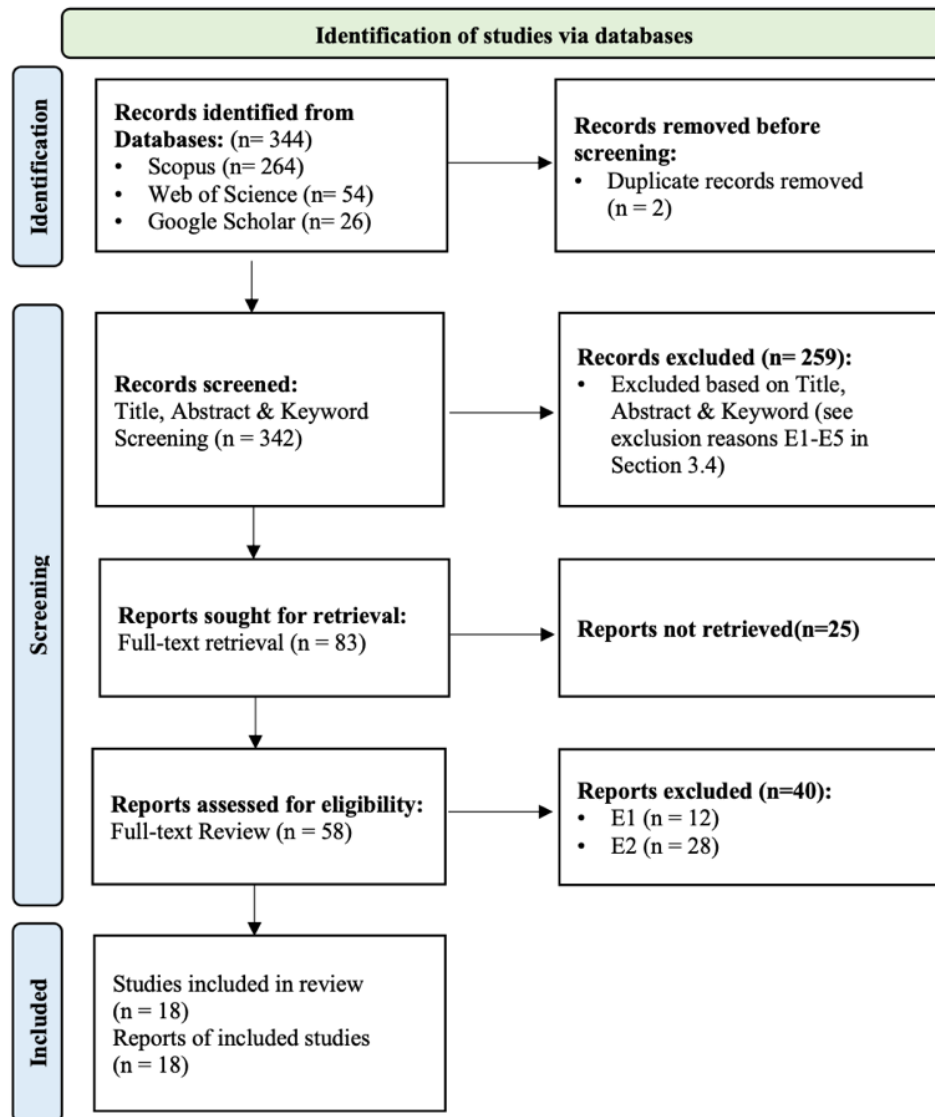


Fig. 1. PRISMA Flow Diagram

2.2 Search Strategy

Literature searches are mainly conducted on three internationally renowned academic databases: Scopus and Web of Science (WoS), both of which include large numbers of peer-reviewed, high-quality journal articles and provide representative research findings. Additionally, because some relevant studies may not be included in the above databases, Google Scholar is used as a supplementary search tool to enhance the integrity of the literature search and reduce the likelihood of missing related studies. The search strategy in this study was developed based on the research topic and structured around three core concepts: Digital Twin, Pharmaceutical Supply Chain, and Supply Chain Resilience. To expand the coverage of search results, in addition to “Digital Twin,” the search also includes related concepts and synonyms such as “Digital Shadow”, “Cyber-Physical System”, “Virtual Twin”, “Simulation”, “Digital Model”, and “Smart Manufacturing” were derived

from [21]; for the pharmaceutical supply chain, the search includes keywords such as “pharmaceutical,” “pharma,” and “drug.” were established based on [22, 23]. Each keyword is combined using the Boolean operators AND and OR to create a comprehensive and consistent search query.

The search method used in this study in the Scopus database is as follows:

TITLE-ABS-KEY ((“Digital* Twin*” OR “Digital Shadow” OR “Artificial Intelligence” OR “synchronization” OR “cyber-physical system” OR “data model” OR “digital twin platform” OR “virtual twin” OR “Simulation” OR “Real-time simulation” OR “Real-time control” OR “Digital model” OR “Virtual model” OR “Cloud and Enterprise Systems” OR “3D Model” OR “Digital Model” OR “Real-Time Data” OR “Virtual Twin” OR “Digital Representation” OR “Smart Manufacturing” OR “Virtual Prototyping”))

AND

("supply chain resilience" AND ("pharmaceutical" OR "pharma" OR "Drug"))

After completing the literature search, the retrieved pool was filtered according to the eligibility criteria. This study includes peer-reviewed journal articles and review articles written in English. While no lower boundary on publication year was artificially imposed during the search strategy, 2014 naturally emerged as the earliest retrieved publication meeting all specific search criteria, establishing an effective temporal coverage period of 2014 to 2026.

2.3 Inclusion and Exclusion Criteria

After completing the literature search strategy, this study further established inclusion and exclusion criteria to filter literature that meets the research objectives and maintain consistency and objectivity in the literature selection process. The purpose of these criteria is to screen literature that is highly relevant to the research topic and of academic quality, and to ensure that the final included research effectively addresses the research questions of this study. This study mainly focuses on the application of DT to the resilience of pharmaceutical supply chains. Therefore, the inclusion criteria cover not only research topics, application areas, and research content, but also specific publication parameters including English language, peer-reviewed journal and review articles, and the publication period (2014–2026). The exclusion criteria are used to exclude literature unrelated to the research topic, non-peer-reviewed publications, non-English studies, or those that cannot meet research needs. Table 2 presents the inclusion and exclusion criteria, and screening codes adopted for the literature in this study.

Table 1
Eligibility Criteria

Category	Inclusion Criteria	Exclusion Criteria	Code
Publication year	Published between 2014 and 2026	Published before 2014	-
Document type	Journal articles and review articles	Conference papers, book chapters, editorials, notes, letters, and other non-peer-reviewed publications	-
Language	English	Non-English publications	-
Digital Twin	Studies related to DT technologies	Studies without a DT focus	I1/E2
Supply Chain	Studies related to supply chain or logistics	Studies without a supply chain or logistics focus	I2/E5
Industry	Pharmaceutical supply chain or	Studies focusing on non-pharmaceutical	I3/E1,

	healthcare medicines, drugs, vaccines, or other medical products	logistics involving industries		E4
Resilience	Studies addressing supply chain resilience, disruption, risk, recovery, or related resilience concepts	Studies without a resilience-related focus	I4/E3	

Following PRISMA 2020 guidelines, explicit screening codes were established to record evaluation decisions and exclusion reasons across the title, abstract, and full-text review stages, ensuring methodological consistency and traceability. Through sequential steps: duplicate removal, title and abstract screening, and full-text eligibility review, only studies fulfilling all inclusion criteria were retained for subsequent data extraction.

2.4 Data Extraction

This study systematically extracted data from the 18 finalized studies. This study uses Notion to build a literature database as a data extraction tool. Based on a pre-designed data extraction framework and a standardized coding matrix defining key bibliographic, methodological, and thematic variables, the content is read and organized one by one. In addition to recording basic bibliographic information, the database also creates corresponding fields based on the four research questions (RQ1–RQ4) to facilitate subsequent systematic analysis. Basic bibliographic information includes Title, Author, Year of Publication, Database, Methodology, and DOI. The research content is categorized into the following: DT Application Areas (RQ1), Supply Chain Resilience Capability (RQ2), Evaluation Methods (RQ3), Research Gaps (RQ4), and Future Research Opportunities. Additionally, each document is accompanied by abstracts and research notes to help researchers quickly review and cross-check the research content during analysis.

Table 2
Data Extraction Framework

Data Category	Extracted Information
Bibliographic Information	Title, Author(s), Publication Year, Database, DOI
Study Characteristics	Research Methodology
RQ1	DT Application Area
RQ2	Supply Chain Resilience Capability
RQ3	Evaluation Method
RQ4	Research Gap
RQ4	Future Research Opportunities
Supporting Information	Abstract, Research Notes

3. Results

The comprehensive, systematic literature screening process for this study (including 18 core articles) was detailed in the previous section and covered three major databases: Scopus, Web of Science (WoS), and Google Scholar. To reveal the conceptual structure and thematic clusters inherent in the final version of the literature review database, we use VOSviewer to conduct a keyword co-occurrence analysis.

3.1 Keyword Co-occurrence Analysis

nodes in the Pharmaceutical Supply Chain network are relatively small, indicating that current digital twin research still focuses on general supply chain and smart manufacturing scenarios, with limited research focused on the pharmaceutical supply chain. These results are consistent with the systematic literature review of this study and further highlight the importance and research value of exploring the resilience of digital twins in pharmaceutical supply chain applications.

3.2 Descriptive Analysis

According to the Data Extraction Framework, Table 3 summarizes the basic information for the 18 core papers ultimately included. To enhance the readability and logical depth of the overview, this table has been refined to include the authors and years of the literature, the main application contexts of DT, and the research methods used. As for the specific outputs and answers from each study on the core issues (RQ1-RQ4) of this study, an in-depth thematic review and discussion will be provided in the next section.

Table 3

Overview of included studies and fundamental characteristics

Author(s) & Year	Application Context (DT Application Area)	Research Methodology
[24]	Cold Chain, Manufacturing Planning, Predictive Disruption Management	Literature Review
[25]	Risk Monitoring, Supply Chain Monitoring	Scoping review
[26]	Stress-testing and Disruption Management	Literature Review
[15]	Deviation Detection, Distribution Optimisation, End-to-End Visibility	Case Study, Systematic Analysis
[27]	Controlled Substance Management, Inventory Management	Case Study, Framework
[28]	Distribution Optimisation, Smart Manufacturing, Tracking Systems	Case Study, Qualitative Approach
[12]	Inventory Management in Healthcare	Hybrid proactive-reactive model
[20]	Manufacturing Planning, Quality Control, Risk Assessment	Systematic Literature Review (PRISMA)
[29]	Distribution Optimisation, Manufacturing Planning	Two-stage Optimization Methodology
[30]	Cold Chain Monitoring, Emergency Response, Inventory Management	Case Study, Qualitative Approach
[31]	Capacity Assessment, Risk Monitoring, Scenario Analysis	Mathematical Model
[32]	Distribution Optimisation, Inventory Management, Quality Control	Framework, Simulation
[33]	Distribution Optimisation, End-to-End Visibility, Predictive Analytics	Case Study, Mathematical Model, Simulation
[13]	Cold Chain Monitoring, Distribution Optimisation, Scenario Analysis	Case Study, Simulation
[17]	Demand Forecasting, Distribution Optimisation, Risk Monitoring	Framework, Simulation
[4]	Healthcare Operations, Supply Chain Monitoring	Systematic Literature Review (PRISMA, TOE)
[19]	End-to-End Visibility, Manufacturing Planning	Case Study, Literature Review
[34]	Demand Forecasting, Inventory Management, Quality Control	Systematic Literature Review

3.3 Contextual Characteristics

The 18 core papers included in this study show that the application of Digital Twins (DT) covers multiple key nodes in the pharmaceutical supply chain, including manufacturing and production, inventory management, logistics and distribution, cold chain management, as well as hospitals and end-point medical institutions, covering the supply chain processes from upstream raw material supply and midstream pharmaceutical production and distribution to downstream medical institutions and patients. However, the research focus is uneven, with logistics distribution and cold chain management receiving the most attention. Most studies combine IoT and digital twin technologies to monitor vaccines and other perishable medical products in real time, improving product quality and safety during transportation; In contrast, research on manufacturing process optimization, hospital-side operations management, and cross-node integration is relatively limited. Regarding disruption scenarios, existing literature mainly focuses on public health events such as COVID-19, drug shortages, cold chain disruptions, and market demand fluctuations. Digital twins are used for scenario simulation and stress testing to evaluate supply chain performance and response capabilities under different risk events. Overall, current research on pharmaceutical supply chain resilience in digital twins mainly focuses on specific supply chain nodes such as logistics and cold chain, as well as common disruption scenarios like pandemic impacts, drug shortages, and cold chain failures, while research covering the entire supply chain process remains relatively limited.

3.4 Research Method Distribution

By methodologically breaking down the 18 core articles selected in this study, the research approaches can be summarized into five major categories, as shown in Table 4.

Table 4
Research Method of Included Studies

Method	Number
Systematic Literature Review & Conceptual	7
Simulation Modeling & DT Architecture	5
Mathematical Optimization & MCDM	3
Qualitative Research & Interviews	2
Mixed-Methods	1

Table 4 summarizes the research methods adopted by the 18 included studies. Five main methodological categories were identified. Systematic literature reviews and conceptual studies were the most common ($n = 7$), followed by simulation modeling and DT framework development ($n = 5$). Mathematical optimization and multi-criteria decision-making methods accounted for three studies, while qualitative research and interviews ($n=2$) and mixed-methods research ($n=1$) were comparatively less common.

Conceptual and systematic literature review studies mainly synthesized existing knowledge, identified research trends, and proposed conceptual frameworks for DT implementation [4, 20, 26]. These studies provide a theoretical foundation for understanding DT applications in pharmaceutical

supply chains but do not validate DT performance in operational settings. Simulation-based studies employed Discrete Event Simulation (DES), Agent-Based Modeling (ABM), and Digital Twin architectures to evaluate supply chain performance under different disruption scenarios [12]. These approaches enable researchers to test alternative strategies without interrupting real-world operations. Mathematical optimization studies used mixed-integer programming (MIP), fuzzy logic, and MCDM techniques to optimize inventory allocation, production planning, and transportation decisions under uncertainty [12, 29, 4, 31]. Qualitative and mixed-methods studies relied on interviews, case studies, and expert opinions to investigate organizational, technological, and regulatory challenges associated with DT implementation [28, 30].

Unlike modeling or optimization studies that evaluate specific DT applications, this study adopts a systematic methodological literature review. This study is not about developing a new DT model, but rather clarifies application areas, resilience capabilities, assessment methods, and research gaps in the pharmaceutical supply chain through a review and comparison of existing evidence. Although various research methods have been adopted, qualitative and mixed methods studies remain relatively limited. Future research could combine simulation models with empirical case studies or stakeholder interviews to more effectively assess the implementation of DT in actual pharmaceutical supply chain environments.

3.5 Results by Research Questions

This section analyzes and summarizes the 18 final papers based on the four Research Questions (RQs) proposed in this study, exploring the current application status of DT in the pharmaceutical supply chain. The analysis results of each research question are presented in subsequent sections to comprehensively reflect the objectives of this study.

3.5.1 Digital Twins Application Area (RQ1)

This section aims to answer the first research question and explore the main application areas of DT in the pharmaceutical supply chain. A comprehensive review of 18 included studies reveals that DT technology has been applied across multiple stages of the pharmaceutical supply chain, which is categorized into six core areas: Manufacturing and Production, Inventory Management, Logistics and Distribution, Cold Chain Management, Quality Management, and End-to-End Supply Chain Management. A review of the included literature shows that most studies focus on real-time data monitoring [13, 14, 30, 32] and information integration [19, 24, 17]. Additionally, computer simulations are widely adopted as core analytical methods for evaluating digital twin applications across different supply chain disruption scenarios [12, 15, 17, 31, 33].

In the upstream fields of "Manufacturing and Production" and "Quality Management", DT have been applied to support production optimization, process monitoring, and quality assurance. For example, by establishing mechanistic models for continuous manufacturing and micro factories, waste of active pharmaceutical ingredients (APIs) can be effectively reduced and quality control optimized [19]. However, the practicality of these in-plant applications is often overly idealized. Implementing smart manufacturing systems that combine artificial intelligence and DT may require substantial upfront investment. This high financial threshold not only widens the technological gap between

large multinational pharmaceutical companies and small and medium-sized enterprises but also hinders the widespread adoption of such applications in resource-constrained real-world environments [20]. Moreover, most of these models have default production parameters in steady state and rarely explore how in-house DT can dynamically coordinate capacity with external supply chains during raw material shortages or geopolitical disruptions.

In the mid- and downstream supply chain sectors such as "Inventory Management," "Logistics and Distribution," and "Cold-chain Management," the practical application of DT is more urgent and concrete, mainly due to the zero tolerance for temperature-control failures in vaccines and biologics. Research shows that DT integrated with the Internet of Things (IoT) can monitor transportation temperatures in real time and dynamically plan alternative routes, significantly reducing the risk of spoilage and stockouts in perishable medical products [27, 30]. To prevent drug shortages, some prospective studies have also attempted to integrate EHRs, insurance claims, and logistics telemetry data to build big-data predictive early-warning systems [17].

Table 1.

DT Application Areas in the Pharmaceutical Supply Chain

Application Area	Representative Studies
Manufacturing and Production	[12, 19, 20, 24, 29]
Inventory Management	[17, 25, 30, 32, 34]
Logistics and Distribution	[15, 27, 28,31]
Cold Chain Management	[13, 24, 30, 32]
Quality Management	[27, 32, 34]
End-to-End Supply Chain Management	[4, 15, 17, 26, 33]

Finally, in terms of "End-to-End Supply Chain Management," several studies have proposed integrating intelligent Digital Twins (iDT) with blockchain to enable end-to-end visibility and coordination across suppliers, manufacturers, distributors, and healthcare providers [26].

3.5.2 Supply Chain Resilience Capabilities (RQ2)

This section analyzes RQ2 and explores how applying DT in the pharmaceutical supply chain enhances resilience. Based on the analysis of 18 included studies, DT are not only applied to operational management at various stages of the supply chain but also strengthen the supply chain's ability to respond to uncertainties and emergencies through real-time data integration, simulation analysis, and decision support functions. The literature review shows that DT primarily support five core resilience capabilities: Visibility & Traceability, Predictive Proactivity & Early Warning, Adaptability & Flexibility, Robustness & Disruption Recovery, and Regulatory Compliance & Quality Integrity, these capability categories were derived by grouping similar DT applications reported across the reviewed studies according to their primary contribution to supply chain resilience.

From the perspective of resilience evolution, "Visibility & Traceability" is among the most frequently

mentioned resilience capabilities and forms a crucial foundation for many DT applications. In the past, pharmaceutical networks were highly fragmented, but DT eliminates information asymmetry among nodes by mapping physical product flows in real time, thereby effectively suppressing the whip and ripple effects triggered by interruptions [28, 34]. However, visibility alone does not create substantial resilience; the system must further demonstrate predictive, proactive warning capabilities. DT can use big data analytics to capture weak risk signals, minimizing the traditional supply chain's time-to-react, and even providing early warnings before shocks occur. This capability allows managers to extend the system's time to survive and activate defense mechanisms before resources run out [17, 26].

When interference occurs, the "Adaptability & Flexibility" supported by DT, as well as "Robustness & Disruption Recovery," become key factors in determining whether the system can quickly bounce back. Unlike traditional static redundancy, the quantitative models [12, 31] demonstrate how DT can perform parallel computing in virtual environments, quickly identifying the best capacity recovery or lateral transshipment strategies among thousands of alternatives. This not only strengthens the system's ability to absorb extreme shocks but also significantly shortens the time-to-recover (TTR) period. However, a comprehensive review of the included literature shows that most highly agile refactoring algorithms rarely address the healthcare industry's requirements for regulatory compliance and quality integrity, so this aspect still requires further verification. For example, research by [13, 32] pointed out that while DT can continuously monitor quality and prevent counterfeit drugs during disruptions, in practice, any changes to dynamic processes or unauthorized supplier switches without prior validation may directly violate GMP regulations. Therefore, some refactoring strategies proposed by DT may be subject to regulatory restrictions.

Table 2.

Resilience Capabilities Supported by DT Implementations

Resilience Capability	Representative Studies
Visibility & Traceability	[13, 15, 19, 27, 28, 34]
Predictive Proactivity & Early Warning	[17, 24, 26, 30, 32]
Adaptability & Flexibility	[12, 20,31, 32, 33]
Robustness & Disruption Recovery	[4, 12, 25,29,31]
Regulatory Compliance & Quality Integrity	[13, 24, 27, 32]

In summary, the greatest contribution of DT to pharmaceutical supply chain resilience lies in elevating defense mechanisms from static physical buffers to dynamic digital intelligence. By enhancing visibility and predictive warning, it effectively extends the system's survival time in the face of crises; Virtual algorithms also provide the network with high adaptability and refactoring capabilities, accelerating recovery after outages. The literature analysis shows that the main contribution of DT to pharmaceutical supply chain resilience lies in enhancing visibility, predictive capabilities, adaptability, and resilience to outages.

3.5.3 Evaluation Methods of DT Applications (RQ3)

This section addresses the third research question by examining how Digital Twin applications have been evaluated in the reviewed literature. This section focuses on the approaches used to evaluate the effectiveness and performance of Digital Twin applications. Four evaluation approaches were identified: (1) simulation-based scenario analysis, (2) conceptual framework validation, (3) mathematical optimization and algorithm benchmarking, and (4) empirical case studies and qualitative validation.

Simulation-based scenario analysis is the most common evaluation method used in the included literature. Most studies use DT to build virtual models of the supply chain, simulating different operational scenarios and supply chain disruption events, such as demand fluctuations, equipment failures, logistics delays, or raw material shortages, to evaluate the effectiveness of DT in enhancing supply chain resilience and decision support. Through scenario simulation, researchers can compare the impact of different decision strategies on supply chain performance and analyze the application potential of DT in risk prediction, resource allocation, and process optimization. Although simulation is the primary assessment method used in the studies included in this review, simulation research is not the same as digital twin research. Traditional simulation research typically uses static models to analyze predefined scenarios, whereas digital twin research integrates simulation models with real-time data and continuous data updates to reflect the ever-changing state of physical systems throughout their lifecycle [15, 19]. In this context, simulation is the core evaluation mechanism in digital twins, rather than representing the digital twin itself. Compared with direct testing in real pharmaceutical supply chain environments, simulation analysis offers advantages such as lower cost, lower risk, and repeatability for verification, making it the most widely used evaluation method today.

In addition to simulation-based evaluation and algorithm benchmarking, conceptual framework validation is another evaluation approach identified in the reviewed literature [19, 24]. Rather than measuring operational performance directly, these studies evaluate the feasibility, system architecture, and implementation readiness of proposed Digital Twin (DT) applications prior to practical deployment [4, 20]. Typically, they present multi-layer system architectures or technology integration models that illustrate how enabling technologies, including artificial intelligence (AI), the Internet of Things (IoT), blockchain, and cloud computing, can be integrated to support intelligent pharmaceutical supply chain management [20, 24, 26, 34]. Therefore, conceptual framework validation primarily assesses the logical consistency, technological integration, and implementation feasibility of proposed DT systems rather than their operational performance in real-world environments.

To overcome the limitations of pure simulation models and further verify algorithm performance, some scholars have turned to mathematical optimization and benchmarking algorithm testing. For example, Manoharan & Sharm [32] rigorously quantified the CPU time and product loss rate of their Hybrid Integer Programming (MIP) DT model against traditional benchmark strategies; Kayhan et al.

[29] and others used a fuzzy optimization model combining best and worst methods (FF-BWM) for quantitative evaluation to measure the mathematical superiority of the strategy. Although such benchmarking tests effectively demonstrate the advantages of DT algorithms in minimizing costs and computational efficiency, existing research rarely discusses the communication latency and infrastructure costs involved in real-time data synchronization. Some studies use case studies to evaluate DT applications, analyzing the effectiveness of DT in real-world operations across specific enterprises, supply chain processes, or pharmaceutical production scenarios. Compared to simulation studies, case studies provide more practical validation results to help evaluate the impact of DT on supply chain visibility, risk management, and decision-making efficiency. However, the number of related cases remains relatively limited, with most research still at the proof-of-concept or small-scale application stages, indicating that there is still room for further development in the practical implementation of DT in the pharmaceutical supply chain.

Table 3.

Evaluation Approaches of DT Applications in Pharmaceutical Supply Chains

Evaluation Approach	Representative Studies
Simulation & Scenario Analysis	[12,13, 17, 33]
Conceptual Framework & Maturity Assessment	[15, 24, 4, 34]
Empirical Case Studies & Qualitative Validation	[19, 27, 28, 30]
Mathematical Optimization & Algorithm Benchmarking	[29,31, 32]

3.5.4 Research Gap and Future Opportunities (RQ4)

Based on the analysis of RQ1 to RQ3, this study identified three major research gaps from the 18 included studies. First, most current research still focuses on the technical development, simulation analysis, and optimization models of digital avatars (DT), with relatively limited exploration of non-technical issues such as organizational factors, personnel decision-making, and cross-departmental collaboration. However, the pharmaceutical supply chain involves multiple stakeholders such as manufacturers, logistics providers, medical institutions, and regulatory agencies. In public health events or supply disruption scenarios, fluctuations in demand, decision-making biases, cross-organizational coordination efficiency, and personnel acceptance of new technologies can all affect the successful implementation of DT applications. Therefore, future research should place greater emphasis on the impact of human factors and organizational management factors in the DT implementation process [20, 25, 30].

Second, existing research generally assumes that data can be shared in real time and completely among supply chain nodes to support DT's real-time monitoring and decision-making functions. However, the pharmaceutical supply chain consists of multiple independent organizations such as API suppliers, manufacturers, logistics providers, medical institutions, and government regulatory agencies. There are constraints among different stakeholders such as commercial competition, data security, and regulatory compliance, making cross-organizational data sharing and collaboration

significant practical challenges. Therefore, how to establish effective cross-organizational collaboration and information sharing mechanisms while safeguarding data security and business secrets remains an important research direction for future DT applications [4, 15, 24].

Third, the literature mainly focuses on technical indicators such as supply chain performance, cost reduction, operational efficiency, and resilience improvement, while there is relatively insufficient discussion of regulatory compliance, governance mechanisms, and post-implementation management issues. As DT applications are increasingly used to support decision-making, its impact on medical resource allocation, supply chain decision-making, and quality management are becoming increasingly important. Therefore, future research should not only continuously verify the technical benefits of DT but also incorporate governance, regulations, and practical implementation for more comprehensive evaluation. These regulatory and governance-related issues will be further discussed in the next section, Policy Document Evaluation.

3.6 Policy Document Evaluation

To bridge the gap between academic literature and practical implementation, this study extends its analytical perspective to 13 core policy documents issued by global regulatory agencies and international organizations, comparing regulatory priorities in academic research development and practice, and answering research questions 1-4. These policy documents come from organizations such as the World Health Organization (WHO), the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the European Commission, the UK Medicines and Healthcare Products Regulatory Agency (MHRA), and the Korean Ministry of Food and Drug Safety (MFDS).

The comprehensive policy documents included show that the application of DT and related artificial intelligence (AI/ML) technologies in the pharmaceutical supply chain mainly focuses on smart manufacturing, supply chain management, pharmacovigilance, and sustainable development. Among them, the U.S. Food & Drug Administration [40] noted that DT can use digital models for process simulation, optimized process design, and Advanced Process Control (APC), thereby supporting equipment monitoring, predictive maintenance, and real-time decision-making. Additionally, AI/ML is applied in demand forecasting, production scheduling analysis, inventory optimization, and supply chain disruption risk prediction to enhance supply chain operational efficiency. In post-market management, it also emphasizes the use of artificial intelligence, natural language processing (NLP), and real-world data (RWD) to support pharmacovigilance and adverse event monitoring [35, 36]. The Medicines Manufacturing Industry Partnership (MMIP) [37] further proposed applying digital technologies to pharmaceutical recycling and circular supply chains to enhance supply chain sustainability and reduce environmental impact.

When discussing the supply chain resilience capabilities (RQ2) supported by DT, policy documents show that DT and related digital technologies mainly support stable operations in the pharmaceutical industry by enhancing supply chain resilience. Their core capabilities include interruption prevention, quality management, regulatory compliance, cybersecurity, and governance mechanisms. The FDA's Quality Management Maturity (QMM) program emphasizes reducing shortage risks through digital management, while AI/ML support predicts supply chain disruptions and mitigates risks, enhancing supply chain reliability [35, 38]. Additionally, multiple policy documents emphasize the importance of quality management and regulatory compliance. For example, the (International Medical Device Regulators Forum, [39] establishes Good Manufacturing Practice (GMP) for digital healthcare products

based on ISO 13485 to ensure product quality and safety. At the same time, the policy incorporates cybersecurity as a key requirement for the DT' lifecycle management and, through human-led governance, risk management, and accountability, ensures that the application of digital technologies meets security, legal, and ethical requirements.

For digital applications (RQ3), compared with academic literature, which mostly uses simulation analyses and case studies to evaluate DT, policy documents place greater emphasis on model validation, regulatory validation, and regulatory requirements. The European Medicines Agency [35] requires AI models to be validated using test datasets that are completely disconnected from development data, ensuring good external validity and generalization capability; U.S. Food & Drug Administration [40] adopts the V&V 40 (Verification and Validation) framework to evaluate the credibility of computational models and AI/ML systems, comprehensively considering model design, algorithm selection, and performance metrics. In addition, policy documents emphasize the need to establish comprehensive risk management and audit mechanisms to ensure transparency and traceability of model decisions. The International Medical Device Regulators Forum [39] in Korea encourages the integration of Real-World Evidence (RWE) and decentralized clinical trials (DCT), serving as an important basis for evaluating digital health technologies.

Finally, regarding existing research gaps and future development opportunities (RQ4), the policy document notes that DT and AI technologies still face multiple challenges in their development, including algorithmic transparency, bias management, regulatory innovation, and the application of emerging technologies. U.S. Food & Drug Administration [40] points out that improving model explainability and establishing transparent algorithmic governance mechanisms are key directions for promoting AI applications in healthcare. At the same time, effective mechanisms for bias identification and management must be established to enhance model fairness and reliability. Additionally, [36] is actively exploring the application of generative AI and large language models (LLMs) in pharmacovigilance and regulatory processes. Overall, the policy document indicates that the future development of DT will focus not only on enhancing technical capabilities but also on governance structure, regulatory systems, and cross-departmental collaboration to support its practical application within the pharmaceutical supply chain.

Table 8.

Summary of Findings from Academic Literature and Policy Documents

Research Question		Academic Literature	Policy Documents
RQ1: Application Areas		Node-specific focus (e.g., cold chain monitoring, in-plant optimization).	Macro-level focus (e.g., advanced manufacturing, national digital health infrastructure).
RQ2:	Resilience Capabilities	Emphasizes dynamic adaptability, predictive early warning, and minimizing recovery time.	Prioritizes regulatory compliance, data integrity (ALCOA+), and cybersecurity.
RQ3:	Evaluation Methods	Primarily relies on computer simulations and mathematical optimization.	Mandates rigorous regulatory validation and continuous real-world data monitoring.
RQ4: Research Gaps & Future		Highlights gaps in cross-organizational data sharing, socio-technical models, and bioethics.	Focuses on Trustworthy AI, algorithm explainability (XAI), and human-in-the-loop governance.

Table 8 compiles the main findings from academic literature and policy documents. Overall, both emphasize the importance of digital technologies in enhancing the resilience of pharmaceutical supply chains but differ in their research focus and evaluation perspectives.

4. Conclusions

This study synthesizes the application areas, resilience capabilities, evaluation methods, and future directions of Digital Twins (DT) in pharmaceutical supply chains. The literature review shows that DT is increasingly being applied across various critical areas of the pharmaceutical supply chain, including manufacturing process optimization, cold-chain logistics monitoring, inventory management, quality assurance, and end-to-end supply chain integration. Among these, applications such as cold chain logistics, demand forecasting, real-time risk warning, and disruption recovery have received significant academic attention, such as [12, 13, 26, 30, 33]. By integrating real-time data, simulation models, and predictive analytics, DT can strengthen key capabilities for supply chain resilience, including visibility, proactive risk management, adaptability, robustness, and disruption recovery. This suggests a potential shift from a passive inventory buffer model that relied mainly on safety stock to a more dynamic, data-driven, and proactive decision-making model. However, there is still a significant gap between the technical vision presented by academic research and the actual application reported in current literature. Many of the DT applications reported in the literature remain at a one-way data synchronization and real-time monitoring level rather than two-way autonomous control. Moreover, current academic research heavily relies on computer simulation methods, such as Discrete-Event Simulation (DES) and Agent-Based Modelling (ABM), as well as mathematical optimization methods like Mixed-Integer Programming (MIP). These methods are usually built on more simplified or idealized assumptions, so they do not fully reflect the limitations and complexities of real operating environments.

In contrast, global regulatory policy documents focus on different topics than academic research, emphasizing regulations, data integrity, and cybersecurity issues. Regulators emphasize the use of real-world data and the adoption of verification and validation methods to ensure the credibility, traceability, and security of digital models. This reflects a significant distinction between academic research and policy practice. Academic literature tends to prioritize algorithmic performance and operational optimization, while policy documents place greater emphasis on regulatory safety, procedural compliance, and the credibility of digital systems in real-world environments.

The research results show that the development of DT in the pharmaceutical supply chain is not only limited by technology but also influenced by data, organization, and regulatory factors. Academic research widely confirms that DT can enhance supply chain visibility, predictive capabilities, logistics management, and resilience through simulation, optimization, and real-time data [12, 17, 24, 30]. However, many models are built under relatively simplified conditions, such as assuming stable data circulation, effective information sharing between organizations, and a certain degree of predictability in supply chain behavior. The pharmaceutical supply chain faces issues such as data silos, difficulties in integrating existing systems, high implementation costs, and insufficient trust among different stakeholders. Therefore, many applications reported in the literature are still at the Digital Shadow or real-time monitoring stage and have yet to achieve complete autonomous closed-loop control [15, 19]. This means that simply improving DT technology and model performance may not be enough to achieve a resilient DT supply chain.

Moreover, the characteristics of the pharmaceutical industry make DT implementation more complex than general manufacturing. The pharmaceutical supply chain is a social and technological system. Digital technologies not only need to have strong technical performance but also meet strict quality and regulatory requirements. Policy documents from the FDA, EMA, and WHO all emphasize requirements for data integrity, model validation, risk management, and cybersecurity [35,40,41].

Decisions and recommendations generated by DT, such as inventory reallocation or production and distribution adjustments, must also comply with GMP, GDP, quality, and relevant regulatory requirements [20, 42]. Additionally, cross-organizational data governance, change management, and personnel factors also influence the practical application of DT. Therefore, DT adoption in the pharmaceutical supply chain is not just about technological transformation; it also involves organizational and regulatory challenges.

The future development of DT should move toward more trustworthy and governable systems. In high-risk environments like pharmaceuticals, DT are more suitable as an intelligent decision support tool with personnel supervision, rather than a fully autonomous decision-maker. At the same time, future research should focus on privacy protection technologies required for cross-organizational data sharing, as well as standardized architectures and data protocols to enhance system interoperability. Overall, the successful development of a pharmaceutical supply chain DT requires balancing technical capability, operational efficiency, regulatory compliance, and personnel governance.

This study bridges two relatively fragmented research areas: DT and pharmaceutical supply chain resilience. Current DT research mostly focuses on smart manufacturing, Industry 4.0, or general supply chain management, while systematic studies on how DT supports pharmaceutical supply chain resilience remain relatively limited. This study further supplements research in this field by integrating relevant literature to establish a knowledge base for DT applications in the pharmaceutical supply chain. Second, this study establishes an "Application–Capability" analysis link, linking different DT application scenarios to supply chain resilience. For example, cold chain monitoring mainly enhances supply chain visibility [13, 32], smart manufacturing and capacity management help improve adaptability [29], while scenario simulation and risk prediction support disruption recovery [12]. This analysis helps illustrate how DT technology translates into concrete supply chain resilience capabilities and provides a foundation for future related research. Finally, this study incorporates the policies and guidelines of regulatory agencies worldwide into the analysis, focusing not only on the technical feasibility of DT but also on practical requirements such as data integrity, model validation, traceability, and governance. This helps connect academic research with regulatory practice, broadening the analytical perspective of traditional SLRs. The research results indicate that applications such as cold chain monitoring, inventory management, and manufacturing process management have high potential and can help companies identify priority development areas during digital transformation. Furthermore, this study emphasizes that the main value of DT at this stage is not necessarily full automation, but rather enhancing real-time monitoring, risk warning, and decision support capabilities. Therefore, companies can view DT as management tools to enhance supply chain resilience and decision quality, rather than simply pursuing highly automated technical solutions. At the same time, data integrity, model validation, traceability, and information security requirements outlined in policy documents can serve as important references for enterprises and technology providers during DT design and deployment.

The results of this study show that DT has the potential to enhance the resilience of pharmaceutical supply chains, but its successful implementation depends not only on technological maturity but also on organizational capabilities, data governance, and regulatory environments. Therefore, this section discusses the practical implications of enterprise management and policy regulation based on the research findings.

For pharmaceutical companies, DT should not be seen as a one-time IT investment, but rather as part of a comprehensive supply chain resilience strategy. The research results show that current DT applications are mainly concentrated in cold chain logistics, manufacturing processes, and inventory

management [13, 25, 27]. Therefore, companies can adopt phased deployment strategies, prioritizing DT in high-risk and high-value supply chain segments and gradually expanding to cross-departmental and cross-organizational integrated applications. This helps reduce initial investment risks and accumulate experience in system integration and organizational learning. Additionally, companies should position DT as a decision support tool, rather than a fully autonomous decision-making system. When facing demand fluctuations, supply disruptions, or logistics anomalies, DT can assist managers in evaluating different response plans through real-time monitoring, scenario simulation, and risk prediction. However, this "human-in-the-loop" approach ensures that the final decision should still be made by personnel with specialized knowledge, balancing decision quality with regulatory compliance. Finally, DT implementation needs to evolve in sync with organizational capabilities. Beyond information infrastructure, companies should also strengthen data governance, cross-departmental collaboration, and digital talent development, while promoting collaboration among IT, supply chain management, quality assurance, and regulatory affairs. Only then can DT's technical capabilities be transformed into real supply chain resilience.

4.1 Policy and Regulatory Implications

For policymakers and regulators, establishing a regulatory environment suitable for the deployment of DTs is a key condition for promoting their wider application. Currently, international regulatory agencies are gradually establishing guidelines related to AI and digital models, but there is still room for further development in specialized governance frameworks for DT. First, regulators should continuously improve data governance and model validation requirements, establishing more consistent and transparent standards for data quality, model validation, traceability, and lifecycle management, thereby reducing regulatory uncertainty when enterprises implement DT. Second, cross-organizational data exchange and interconnectivity standards should be further promoted, enabling pharmaceutical companies, logistics providers, medical institutions, and regulatory agencies to share information while ensuring data security and privacy. Finally, since DTs are rapidly evolving emerging technologies, regulators can use mechanisms like regulatory sandboxes or Early Scientific Dialogues to enable companies to test new technologies, conduct model validation, and conduct risk assessments in controlled environments, while also helping regulators accumulate governance experience for emerging technologies.

Overall, the digital transformation of the pharmaceutical supply chain should not focus solely on technological innovation; it also requires the simultaneous development of enterprise management, data governance, and regulatory systems. Companies should view DT as a management tool to improve decision-making quality and supply chain resilience, while policymakers should establish regulatory environments that balance innovation, transparency, and risk governance to help move DT from proof-of-concept towards wider and more trustworthy practical applications.

4.2 Future Research Directions

Future research should first include empirical studies using Real-World Data (RWD) to verify the actual impact of DT on pharmaceutical supply chain resilience. Currently, many studies still rely on simulated data or hypothetical scenarios [4, 15, 19]. In the future, through enterprise cases studies, longitudinal studies, or cross-enterprise collaborations, the effectiveness of DTs under real-world scenarios such as large demand fluctuations, cold chain disruptions, or supplier failures can be

evaluated, and further methods for validating models that meet regulatory requirements can be explored.

Second, cross-organizational data sharing and trust mechanisms remain important research topics in DT development. Future research can explore how Federated Learning, blockchain, and other privacy-preserving technologies can support cross-enterprise data collaboration, enhancing supply chain visibility while maintaining data security and ownership [13]. Third, as the importance of AI in DT increases, future research should focus more on human-in-the-loop and Explainable AI (XAI). The study can further explore how to incorporate expert judgment, regulatory requirements, and ethical considerations into the DT decision-making process to enhance model transparency, traceability, and regulatory acceptance [35, 40]. Finally, future research can further compare regulatory systems across different countries or regions, such as FDA, EMA, MHRA, and major Asian regulatory agencies (such as South Korea's Ministry of Food and Drug Safety) in AI governance, model validation, and data governance, to explore how different regulatory environments influence DT development and adoption in the pharmaceutical supply chain. Overall, the limitations of this study reflect that DT research in the pharmaceutical supply chain is still in a rapidly developing phase. In the future, through real-world data, cross-organizational collaboration, and cross-national regulatory comparisons, along with further deepening AI governance and empirical validation, DT can gradually move from proof-of-concept to more practical, credible, and compliant applications.

Author Contributions

Conceptualization, Homa Molavi and Ju-Ting; methodology, Homa Molavi and Ju-Ting; validation, Homa Molavi and Ju-Ting; formal analysis, Ju-Ting; investigation, Ju-Ting; data curation, Ju-Ting; writing, original draft preparation, Homa Molavi and Seyede Elaheh Molavi; writing, review and editing, Homa Molavi and Ju-Ting; visualization, Homa Molavi; supervision, Homa Molavi; project administration, Homa Molavi. All authors have read and agreed to the published version of the manuscript.

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