Blockchain Technology in Cold Chain Logistics for Pharmaceuticals: A Comprehensive Review

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***Abstract*—The pharmaceutical industry relies heavily on the integrity of its supply chain, particularly for products requiring cold chain management. Maintaining strict temperature ranges during transit and storage is crucial to ensure the efficacy and safety of these sensitive medications. Traditional pharmaceutical supply chains face numerous challenges, including temperature deviations, the infiltration of counterfeit drugs, and a lack of end-to-end transparency. Blockchain technology, with its inherent characteristics of decentralization, immutability, and transparency, presents a potential solution to address these critical issues by offering enhanced traceability, security, and data integrity. This review paper provides a comprehensive analysis of the existing literature on the application of blockchain technology in pharmaceutical cold chain logistics. The methodology involved a targeted search across key academic databases, focusing on peer-reviewed articles published in high-ranking journals that specifically addressed the intersection of blockchain technology and cold chain management for pharmaceuticals. The findings indicate a growing interest in leveraging blockchain to improve key aspects of the pharmaceutical cold chain, from enhancing product traceability and combating counterfeiting to ensuring the integrity of temperature monitoring data. However, the review also highlights significant challenges related to scalability, interoperability, regulatory compliance, and the need for more empirical validation of proposed solutions. To address these limitations, the paper suggests future research directions aimed at further exploring the potential of blockchain technology in this critical domain.**

***Index Terms*—blockchain technology, pharmaceutical cold chain, supply chain management, traceability, drug counterfeiting, IoT integration, temperature monitoring, data integrity, permissioned blockchains, smart contracts, regulatory compliance**

I. Introduction

A. Background

Maintaining the quality and efficacy of pharmaceutical products throughout the supply chain is of paramount importance, especially for medications that require strict temperature control, commonly referred to as cold chain logistics [1]. The sensitivity of pharmaceuticals to temperature variations means that deviations from the prescribed range can significantly reduce their therapeutic effectiveness or render them harmful to patients [1]. Robust and reliable systems are therefore essential to ensure these temperature-sensitive products are stored and transported under optimal conditions from manufacturing to the end consumer. The integrity of the cold chain directly impacts patient safety and public health.

B. Problem Statement

Traditional pharmaceutical supply chains are often complex, involving numerous intermediaries such as manufacturers, distributors, wholesalers, and retailers [3]. This complexity introduces several inherent vulnerabilities. A lack of transparency across these stages makes it difficult to effectively track products and verify their provenance [5]. Furthermore, the pharmaceutical industry is plagued by counterfeit drugs, which not only defraud consumers but also pose severe health risks [7]. The absence of a unified and immutable system for tracking and authenticating pharmaceutical products exacerbates these challenges.

C. Blockchain Technology and its Potential

Blockchain technology has emerged as a disruptive force, offering a decentralized, immutable, and transparent ledger system with the potential to transform various industries [9]. At its core, a blockchain operates as a distributed database shared among multiple participants. Each transaction or piece of information is recorded in a block, and each block is cryptographically linked to the previous one, forming a tamper-proof chain [11]. This decentralized structure eliminates the need for a central authority, fostering trust and transparency among network participants [4]. Consensus mechanisms ensure agreement among participants on the validity of data added to the blockchain, further enhancing reliability [11]. Smart contracts, self-executing agreements written in code and stored on the blockchain, can automate processes and enforce pre-defined rules without intermediaries [11].The application of blockchain technology holds significant promise for addressing the challenges inherent in pharmaceutical cold chain logistics. By providing an immutable and transparent record of a drug's journey, blockchain can enhance end-to-end visibility, enabling stakeholders to track the product at every stage of the supply chain [4]. Moreover, when integrated with temperature monitoring devices, blockchain can ensure the integrity of critical environmental data, providing an auditable history of temperature conditions [11]. This capability is crucial for verifying that cold chain pharmaceuticals have been maintained within required temperature ranges throughout transit. Additionally, blockchain can play a vital role in verifying the authenticity of pharmaceutical products, helping to combat counterfeit drugs and safeguard patient safety [16].

D. Scope and Objective

This review paper aims to provide a comprehensive analysis of the existing academic literature concerning the application of blockchain technology in pharmaceutical cold chain logistics. The objective is to identify key trends, challenges, and opportunities, as well as limitations in current studies, and to suggest potential directions for future research in this rapidly evolving field.

II. Literature Review

A. Enhancing Traceability and Provenance

A significant focus in the literature is on how blockchain technology can revolutionize the traceability of pharmaceutical products within the cold chain [9]. The inherent immutability of blockchain records provides a transparent and auditable history of a drug's journey, from its origin at the manufacturing facility to its final destination with the consumer [4].

1) Key Features of Blockchain for Traceability: Immutable Records: Each step in the supply chain, including manufacturing details, batch numbers, expiration dates, and custody transfers, can be securely recorded on the blockchain, creating an unbroken chain of information that is virtually impossible to tamper with [9].Unique Identifiers: Many proposed blockchain-based solutions utilize unique identifiers, such as QR codes or serial numbers, associated with each pharmaceutical product and recorded on the blockchain [13].Tracking Ownership and Custody: Blockchain facilitates tracking ownership and custody transfer at each point, ensuring accountability and providing a clear record of product handling [14]. This granular traceability represents a significant improvement over traditional systems, where information may be siloed or difficult for different stakeholders to access [6]."One Thing, One Code, One Traceability Code": The concept of "one thing, one code, one traceability code" is highlighted as a means of strengthening drug safety by ensuring that each individual unit of medication has a unique and verifiable identity on the blockchain [9].

2) Examples of Blockchain-Based Traceability Systems: Systems like PharmaChain [19] and Vacledger [20] exemplify this approach, leveraging blockchain's capabilities for secure and rapid transaction recording to establish data provenance and enhance pharmaceutical product tracking. The ability for end-users to verify medication authenticity by scanning QR codes linked to the blockchain empowers patients and fosters greater trust in the pharmaceutical supply chain [16].

B. Combating Counterfeit Pharmaceuticals

Preventing counterfeit and substandard drugs from entering the supply chain is another critical area where blockchain technology offers substantial benefits [7].

1) Role of Immutability in Counterfeit Prevention: The immutability of blockchain records plays a crucial role by ensuring that once drug authenticity information is recorded, it cannot be altered retroactively [4]. This creates a reliable and trustworthy source of information for verifying the legitimacy of pharmaceutical products at any point in the supply chain [14].

2) Consumer Verification and System Examples: Several studies discuss how consumers can potentially verify drug authenticity using blockchain-based systems, often by scanning a QR code on the packaging [15]. This action triggers a blockchain request to verify the product's unique identifier against recorded information, providing instant confirmation of its legitimacy [16]. Systems like PharmaChain utilize on-chain and off-chain storage to securely manage drug authenticity information, while Vacledger focuses on providing a transparent and immutable record for vaccines, helping to prevent counterfeit product circulation [19]. Enabling end-users to directly verify medication authenticity represents a significant step forward in combating counterfeit pharmaceuticals and enhancing patient safety.

C. Ensuring Temperature Monitoring and Data Integrity

Maintaining cold chain integrity requires meticulous temperature monitoring, which can be achieved through the effective integration of blockchain technology with Internet of Things (IoT) sensors [11].

1) Blockchain and IoT Integration: These sensors can continuously monitor temperature and other critical environmental conditions, such as humidity, and securely record this data directly onto the blockchain [12]. The immutable nature of the blockchain ensures that this temperature data remains tamper-proof, providing an auditable and trustworthy record of the environmental history of a batch of pharmaceuticals throughout its journey [24].

2) Role of Smart Contracts: Smart contracts play a vital role in automating actions based on blockchain-recorded temperature data [11]. For example, if a sensor detects a temperature deviation outside the acceptable range, a smart contract can automatically trigger alerts to relevant stakeholders, such as logistics providers or quality control personnel, enabling timely intervention to prevent potential damage to temperature-sensitive products [25].

3) Benefits of Blockchain and IoT Combination: This combination of blockchain and IoT offers a powerful tool for ensuring the quality and efficacy of cold chain pharmaceuticals by creating a transparent, tamper-proof, and responsive system for managing environmental conditions.

D. Enhancing Security and Transparency

The decentralized nature of blockchain technology inherently enhances the security of the pharmaceutical cold chain.

1) Decentralization and Security: By distributing data across multiple nodes, blockchain reduces reliance on central authorities that could be single points of failure [9].

2) Cryptographic Techniques and Access Control: Cryptographic techniques, such as hashing and digital signatures, are employed to ensure the integrity and confidentiality of the data stored on the blockchain [22]. Permissioned blockchains, which require authorized participants to join the network, provide an additional layer of security by controlling access to sensitive supply chain data among trusted stakeholders [7]. This controlled environment helps protect against unauthorized access, tampering, and fraudulent activities, fostering greater trust and transparency among all participants in the pharmaceutical cold chain [18].

E. Interoperability and Data Sharing Solutions

A key challenge in implementing blockchain solutions across complex supply chains is ensuring interoperability between different blockchain-based systems and with existing legacy systems [9].

1) Need for Standardization: The literature highlights the need for standardized data formats and protocols to facilitate seamless data exchange and prevent information silos [10]. One promising approach is the use of verifiable credentials [31].

2) Platforms and Future Research: Platforms like Hyperledger Fabric and Besu are also being explored for their potential to build interoperable solutions, due to their modular architectures and compatibility with various standards [32]. Achieving seamless data exchange between different blockchain networks is crucial for realizing the full benefits of this technology in global pharmaceutical cold chains, and the development of standardized models and interoperability solutions remains an important area of ongoing research.

III. Methodology

This paper employed a systematic literature review to analyze the application of blockchain technology in pharmaceutical cold chain logistics. The review process encompassed the following key stages:

A. Search Strategy

A comprehensive search was conducted across several prominent academic databases relevant to computer science, healthcare, and supply chain management. These databases included:

- IEEE Xplore
- ScienceDirect
- MDPI
- PubMed Central

The search strategy employed a combination of keywords to identify relevant research articles. The primary keywords used were:

- ”blockchain pharmaceutical cold chain”
- ”blockchain drug supply chain”
- ”blockchain temperature monitoring”
- ”blockchain counterfeit drugs”
- ”blockchain healthcare supply chain”
- ”blockchain traceability pharmaceuticals”

B. Selection Criteria

The selection of papers for this review followed predefined criteria to ensure the quality and relevance of the included studies:

- **Journal Quality:** Only articles published in reputable, peer-reviewed journals were considered. Preference was given to journals ranked within the first and second quartiles (Q1/Q2) based on their impact factor or other relevant metrics.
- **Accessibility:** To promote broad accessibility, a focus was placed on selecting open-access articles.
- **Relevance:** The primary criterion for inclusion was the relevance of the paper to the specific topic of blockchain technology in pharmaceutical cold chain logistics. Articles were excluded if they addressed:
  - Blockchain technology in general
  - Pharmaceutical supply chains without a cold chain focus
  - Cold chain logistics in other industries

C. Data Synthesis

The process of synthesizing information from the selected papers involved a thorough reading and analysis of each article. During this process, AI tools, including Claude, Grok, Gemini, and ChatGPT, were utilized to assist in identifying relevant papers and analyzing their content. The synthesis included the following:

- **Thematic Analysis:** Common themes and recurring topics related to the application of blockchain in pharmaceutical cold chain logistics were identified.
- **Comparative Analysis:** Different approaches proposed by researchers were compared and contrasted, focusing on their methodologies, proposed architectures, and key findings.
- **Critical Evaluation:** Specific attention was paid to the challenges and limitations discussed in the literature, as well as the opportunities and potential future directions suggested by the authors.

This systematic approach facilitated the extraction of key data points and the development of a comprehensive understanding of the current state of research in this domain.

IV. Implementation: Technical Architectures and Solutions

The reviewed literature proposes various technical architectures and solutions for implementing blockchain technology in pharmaceutical cold chain logistics. These implementations differ in their choice of blockchain platform, consensus mechanisms, use of smart contracts, integration with IoT devices, and data storage strategies. This section delves into the specific technical details of these proposed solutions, highlighting the advantages and disadvantages of different approaches.

A. Permissioned vs. Permissionless Blockchains

A fundamental decision in designing a blockchain-based system is whether to use a permissioned or a permissionless blockchain.

Permissioned blockchains, such as Hyperledger Fabric, Besu, Quorum, and Corda, require participants to be authorized to join the network [32]. This controlled access offers several advantages for the pharmaceutical cold chain, where data privacy and security are paramount [35]. Permissioned networks can provide strong identity management, ensuring that only trusted entities can access and contribute data to the blockchain [32]. They also often employ more efficient consensus mechanisms compared to permissionless blockchains, leading to faster transaction processing times [37].

TABLE I
COMPARISON OF PERMISSIONED AND PERMISSIONLESS BLOCKCHAINS

Feature	Permissioned Blockchains	Permissionless Blockchains
Access	Restricted to authorized participants	Open to anyone
Privacy	High, strong identity management	Lower, potential privacy concerns
Efficiency	Higher transaction processing speeds	Lower scalability
Control	Centralized control	Decentralized control
Use Cases	Enterprise applications, supply chain	Public ledgers, cryptocurrencies
Examples	Hyperledger Fabric, Besu, Corda	Ethereum, Bitcoin

Permissionless blockchains, like Ethereum and Bitcoin, are open to anyone who wants to participate [36]. While they offer high levels of decentralization and transparency, they may face challenges in terms of scalability and privacy, which can be critical concerns for sensitive pharmaceutical data [39]. However, permissionless blockchains like Ethereum offer robust smart contract functionality and a large ecosystem of developers and tools, which can be leveraged for certain aspects of pharmaceutical cold chain management, such as traceability and authentication using non-fungible tokens (NFTs) [22].

The choice between a permissioned and permissionless blockchain often depends on the specific requirements of the application. Permissioned networks are generally favored for their enhanced privacy and control in enterprise settings like the pharmaceutical industry.

B. Specific Blockchain Platforms

Several specific blockchain platforms are discussed in the literature for their potential in pharmaceutical cold chain logistics.

1) Hyperledger Fabric:

- Designed for enterprise use with a modular architecture [35].
- Supports private channels for data confidentiality [32].
- Uses chaincode (smart contracts) written in Go, Java, and Node.js [43].
- Emphasizes transaction processing efficiency and privacy [44].

2) Ethereum:

- Public, permissionless blockchain known for smart contract capabilities [38].
- ERC token standards (ERC-20, ERC-721) for representing digital assets [39].
- NFTs proposed for enhancing traceability and addressing counterfeiting [13].
- Viable for specific use cases within the cold chain despite potential privacy concerns.

3) Hyperledger Besu:

- Open-source Ethereum client for enterprise use [33].
- Compatible with the Ethereum Virtual Machine (EVM) [48].
- Offers node-level permissioning and pluggable consensus algorithms [49].
- Provides a balance between the public Ethereum ecosystem and enterprise-level control.

4) Gcoin Blockchain:

- Unique governance design with hierarchical roles [50].
- Consortium Proof-of-Work consensus and double-spending prevention [51].
- Drug identification using QR codes generated from batch/serial number hashes [52].

5) NEM Blockchain:

- Features a Smart Asset System for creating custom digital assets [53].
- Employs a Proof-of-Importance (POI) consensus mechanism [55].
- Potential solutions for traceability and supply chain visibility due to its focus on asset management.

C. Smart Contracts and Automation

Smart contracts are a fundamental component of most blockchain-based solutions for the pharmaceutical cold chain [56]. These self-executing contracts automate various processes [11]:

- Recording transactions.
- Verifying temperature conditions.
- Triggering alerts or initiating payments.

By encoding business rules directly into the blockchain, smart contracts enhance efficiency, reduce manual oversight, and ensure tamper-proof agreement execution [13]. For example, they can automatically record temperature excursions or release payments based on cold chain maintenance [26].

D. Integration with IoT and Sensor Technologies

The integration of blockchain with IoT devices is crucial for capturing real-time data on environmental conditions [11].

- IoT sensors monitor temperature, humidity, and location.
- Data is securely transmitted and recorded on the blockchain [57].
- Provides an immutable and time-stamped record of product conditions.

This integration enables continuous monitoring and verification, ensuring that pharmaceuticals are maintained within required temperature ranges [24]. The recorded data supports compliance, quality control, and stakeholder transparency [25].

E. Data Storage and Management

Efficient data management is essential for the scalability and cost-effectiveness of blockchain solutions in the pharmaceutical supply chain [59].

- **On-chain and off-chain storage:** Many implementations use a combination of both [19].
  - Blockchain: Immutable ledger for key transactions.
  - Off-chain (e.g., IPFS): For larger, less frequently accessed data [11].
- **Hybrid approach:** A hash of the off-chain data is stored on the blockchain to ensure data integrity [61].

This strategy reduces the storage burden on the blockchain and improves transaction processing speeds while leveraging its security and immutability.

V. Results and Discussion

A. Comparative Analysis of Different Approaches

The reviewed literature presents a diverse range of blockchain architectures and platforms proposed for pharmaceutical cold chain logistics. Permissioned blockchains, particularly Hyperledger Fabric and Besu, appear to be favored due to the sensitive nature of pharmaceutical data and the need for controlled access among supply chain participants [32]. These platforms offer robust privacy features, customizable consensus mechanisms, and the ability to manage identities, making them well-suited for enterprise-level applications in the highly regulated pharmaceutical industry [35].

In contrast, while permissionless blockchains like Ethereum offer strong smart contract capabilities and have been explored for traceability and authentication using NFTs, their public nature might pose challenges for maintaining the confidentiality of sensitive business and product data [38]. Gcoin blockchain presents a unique approach with its built-in governance model tailored for supply chain management, specifically focusing on combating counterfeit drugs through a consortium-based network [50]. NEM blockchain, with its emphasis on asset management, offers another potential avenue for tracking and tracing pharmaceutical products, although it is less prominently featured in the context of cold chain in the reviewed papers [53].

The choice of blockchain architecture involves trade-offs between several factors. These trade-offs are summarized as follows:

- **Security and Privacy:** Permissioned blockchains generally offer enhanced security and privacy within a controlled environment but might be perceived as less decentralized compared to public blockchains [36].
- **Decentralization and Transparency:** Public blockchains, while highly decentralized and transparent, can face scalability limitations and higher transaction costs, although Layer 2 solutions are being developed to address these issues [63].
- **Cost and Scalability:** The specific needs and priorities of the stakeholders involved in the pharmaceutical cold chain will ultimately dictate the most appropriate blockchain architecture and platform for their particular use case.

Integrating IoT sensors for temperature monitoring is a common theme across many proposed solutions. The data captured by these sensors is typically recorded on the blockchain to provide an immutable record of the environmental conditions [24]. Different approaches exist for how this integration is achieved and how the data is managed on the blockchain, with some solutions utilizing smart contracts to automate alerts and actions based on temperature deviations [11]. Similarly, various methods for uniquely identifying pharmaceutical products are discussed, including the use of QR codes, serial numbers, and NFTs, each with its own advantages and disadvantages in terms of cost, security, and ease of implementation [13].

B. Case Studies and Empirical Findings

While the reviewed literature extensively explores the theoretical benefits and potential applications of blockchain in pharmaceutical cold chain logistics, there is a relative scarcity of real-world case studies and empirical findings that demonstrate the actual effectiveness and impact of these solutions. Some papers present performance metrics, such as throughput, latency, and gas consumption, from simulated implementations of blockchain-based systems [22]. Additionally, cost prediction models have been explored to estimate the financial implications of adopting blockchain technology in the pharmaceutical supply chain [66].

Key observations regarding case studies and empirical findings:

- **Limited Real-World Data:** A significant gap exists in empirical validation through pilot projects and real-world deployments.
- **Simulation-Based Metrics:** Some studies provide performance metrics (throughput, latency) from simulations.
- **Cost Prediction Models:** Cost prediction models for blockchain adoption have been explored.
- **Need for Practical Evidence:** There is a clear need for more empirical validation to assess tangible benefits, challenges, and ROI.

The success of blockchain adoption will ultimately depend on demonstrating its practical feasibility and measurable improvements over existing systems.

C. Challenges and Limitations

The existing research also identifies several challenges and limitations that need to be addressed to facilitate the widespread adoption of blockchain in pharmaceutical cold chain logistics.

1) Technical Limitations: Scalability remains a significant technical hurdle for blockchain technology, particularly in handling the high volume of transactions and data generated across complex global supply chains [63].

- **Scalability Challenges:** While Layer 2 solutions like off-chain processing and sharding offer potential pathways to improve scalability, their maturity and applicability in the context of pharmaceutical cold chain logistics still require further investigation [64].
- **Interoperability Issues:** Ensuring interoperability between different blockchain platforms and integrating them

TABLE II
SUMMARY OF REVIEWED PAPERS AND KEY INFORMATION (PART 1)

Paper Title	Journal	Problem Statement	Proposed Method/Solution	Blockchain Architecture	Validation Approach	Key Findings/Results
Blockchain for drug traceability: Architectures and open challenges.	Health Informatics Journal	Complexity of PSC requires effective traceability to mitigate counterfeit drugs.	Proposes Hyperledger Fabric and Besu architectures for drug traceability.	Hyperledger Fabric, Hyperledger Besu	Analytical comparison	Blockchain offers a potential solution for drug traceability.
A review study of the blockchain-based healthcare supply chain.	Social Sciences & Humanities Open	Improper data management in healthcare supply chain disrupts operations and impacts patient care.	Review of literature on blockchain applications in healthcare supply chain.	Discusses various types (Public, Private, Consortium, Hybrid)	Systematic literature review	Blockchain offers immutability, transparency, and security for healthcare supply chain.
Blockchain technology in supply chain operations: Applications, challenges and research opportunities.	Transportation Research Part E	Traditional supply chains lack transparency and security, leading to inefficiencies and vulnerabilities.	Review of blockchain applications in broader supply chain operations.	Not specified	Literature review	Blockchain can enhance transparency, traceability, and security in supply chains.
A Non-Fungible Token Solution for the Track and Trace of Pharmaceutical Supply Chain.	Applied Sciences	Need for improved track and trace and anti-counterfeiting measures in pharmaceutical serialization.	Proposes an NFT-based solution on blockchain for pharmaceutical serialization.	VeChain Thor	Prototype, Use case	NFT-based solution can strengthen track and trace and improve trust.

TABLE III
SUMMARY OF REVIEWED PAPERS AND KEY INFORMATION (PART 2, CONTINUED)

Paper Title	Journal	Problem Statement	Proposed Method/Solution	Blockchain Architecture	Validation Approach	Key Findings/Results
Governance on the Drug Supply Chain via Gcoin Blockchain.	Int. J. Environ. Res. Public Health	Presence of counterfeit drugs and public distrust in the drug supply chain.	Proposes using Gcoin blockchain for transparent record of drug transactions.	Gcoin Blockchain	Comparison with previous study, Transaction capacity analysis	Gcoin blockchain can enhance security and transparency in drug supply ecosystem.
A Blockchain and Machine Learning-Based Drug Supply Chain Management and Recommendation System for Smart Pharmaceutical Industry.	Electronics	Difficulties in tracking drugs, leading to counterfeit medications.	Proposes a blockchain-based drug supply chain management and recommendation system.	Hyperledger Fabric	Prototype, Testing	Blockchain can efficiently manage and monitor the supply chain process.
PharmaChain: Blockchain-based drug supply chain provenance verification system.	Heliyon	Lack of standardized product traceability in pharmaceutical supply chain, enabling counterfeit drugs.	Introduces PharmaChain, a decentralized Hyperledger Fabric framework for drug traceability.	Hyperledger Fabric	Security analysis (double signing, hash encryption, node attack)	PharmaChain enhances confidentiality, accountability, and interoperability for drug traceability.
Supply chain traceability and counterfeit detection of COVID-19 vaccines using novel blockchain-based Vacledger system.	Expert Systems with Applications	Need for traceability and counterfeit detection of COVID-19 vaccines.	Proposes Vacledger, a blockchain framework with smart contracts for vaccine supply chain.	Private-permissioned blockchain	Use cases, Cost estimation	Vacledger can effectively manage supply chain operations and ensure security.

TABLE IV
SUMMARY OF REVIEWED PAPERS AND KEY INFORMATION (PART 3, CONTINUED)

Paper Title	Journal	Problem Statement	Proposed Method/Solution	Blockchain Architecture	Validation Approach	Key Findings/Results
Blockchain Applications in the Pharmaceutical Industry.	Journal of Medical Systems	Pharmaceutical industry could benefit from blockchain's distributed database and information privacy.	Evaluates potential blockchain applications in pharmaceutical industry using a 4D framework.	Not specified	4D framework analysis	Prescription drug misuse prevention and counterfeit prevention are best applications.
Blockchain technology in the pharmaceutical industry: a systematic review.	PeerJ Computer Science	Lack of transparency, difficulty tracking products, lack of trust, and shipment of expired products.	Systematic review of literature on blockchain adoption in the pharmaceutical industry.	Not specified	Systematic literature review	Blockchain can address issues like counterfeit drugs and improve supply chain.
Blockchain-Based Supply Chain Systems, Interoperability Model in a Pharmaceutical Case Study.	Sensors	Challenge in tracking assets among different blockchain-based supply chain systems.	Proposes an interoperability model using verifiable credentials for tracking assets across different blockchains.	Four different blockchain networks	Case study, Hypothesis testing	Proposed model enables tracking and verification of assets across different blockchain systems.
A blockchain based medicine production and distribution framework to prevent medicine counterfeit.	J. King Saud Univ. - Comp. and Info. Sciences	Mismanagement of supply chains has increased counterfeit medicines.	Proposes a blockchain-based framework to prevent medicine counterfeiting.	Not specified (prototype developed)	Prototype evaluation, Comparison with other systems	Proposed framework is secure, scalable, customer-oriented, and practical.

TABLE V
SUMMARY OF REVIEWED PAPERS AND KEY INFORMATION (PART 4, CONTINUED)

Paper Title	Journal	Problem Statement	Proposed Method/Solution	Blockchain Architecture	Validation Approach	Key Findings/Results
Blockchain Technology in Operations & Supply Chain Management: A Content Analysis.	Sustainability	Increasing examination of blockchain to counter supply chain and operations management challenges.	Content analysis of research on blockchain in operations and supply chain management.	Not specified	Content analysis of 410 articles	Blockchain has potential for tracking, efficiency, and trust-building in supply chain.
Cost Prediction in Blockchain-Enabled Pharmaceutical Supply Chain under Uncertain Demand.	Mathematics	Need for cost prediction models for blockchain-enabled pharmaceutical supply chains under uncertain demand.	Provides a new multi-function mathematical cost model for BT-enabled PSC.	Not specified	Simulation, Algorithm comparison	HS-NB and PSO-NB algorithms perform well in predicting costs.
Blockchain for the Healthcare Supply Chain: A Systematic Literature Review.	Applied Sciences	Growing emphasis on improving SC efficiency in healthcare.	Systematic review of blockchain use in healthcare supply chain.	Not specified	Systematic literature review	Significant but immature interest in the topic, lacking real-life applications.
Blockchain based solution for secure information sharing in pharma supply chain management.	Heliyon	Traditional online pharma systems face issues with transparency and trust.	Proposes a blockchain-based solution for secure information sharing in pharma supply chain.	Ethereum	Security analysis, Performance metrics	Framework effectively mitigates impersonation and collusion attacks.

TABLE VI
SUMMARY OF REVIEWED PAPERS AND KEY INFORMATION (PART 5, CONTINUED)

Paper Title	Journal	Problem Statement	Proposed Method/Solution	Blockchain Architecture	Validation Approach	Key Findings/Results
Blockchain Technology for Detecting Falsified and Substandard Drugs in Distribution.	JMIR Research Protocols	Drug counterfeiting is a global problem with significant risks.	Developing and testing a pharmacosurveillance blockchain system for information sharing.	Ethereum, Hyperledger Fabric	Simulation, Anomaly detection capability	System aims to detect anomalies like missing nodes, invalid certificates, unregistered products.
A Secure Blockchain-based Pharmaceutical Supply Chain Management System: Traceability and Detection of Counterfeit Covid-19 Vaccines.	IEEE Access	Need for a secure and transparent system for tracing and detecting counterfeit COVID-19 vaccines.	Proposes a blockchain-based system for tracking COVID-19 vaccines from manufacturing to end-user.	Not specified	Mobile-based user interface design verification	System enhances reliability, transparency, and security in healthcare data.
Blockchain-based Pharmaceutical Drug Supply Chain Management System.	IEEE Access	Traditional online pharma systems face issues with transparency and mutual trust.	Proposes a blockchain-based solution (BPSCM) implemented in three phases.	Not specified	Security analysis, Performance metrics	Framework effectively mitigates impersonation and collusion attacks.

TABLE VII
COMPARISON OF BLOCKCHAIN ARCHITECTURES

Feature	Permissioned	Permissionless	Gcoin
Access Control	Controlled	Open	Consortium-based
Privacy	High	Low	Medium
Scalability	High	Low	Medium
Consensus	Customizable	Fixed	Tailored for supply chain
Use Cases	Enterprise, regulated industries	Traceability, authentication	Counterfeit drug prevention
Examples	Hyperledger Fabric, Besu	Ethereum	Gcoin

with existing legacy systems also presents considerable technical complexities and costs [70].

- **Security Vulnerabilities** Furthermore, while blockchain offers inherent security features, vulnerabilities can still exist in smart contracts and network configurations, necessitating robust security measures and ongoing monitoring [72].

2) Organizational and Regulatory Hurdles: The adoption of a novel technology like blockchain by established pharmaceutical companies can face organizational inertia and require significant investment in infrastructure and expertise [73].

- **Organizational Inertia:** Resistance to change within pharmaceutical companies can hinder adoption.
- **Stakeholder Collaboration:** Collaboration among diverse stakeholders, with varying technological readiness and potentially conflicting interests, is crucial but challenging [73].
- **Regulatory Uncertainty:** The lack of clear and consistent regulatory frameworks for blockchain technology in the pharmaceutical industry creates uncertainty and can hinder its adoption [72].
- **Compliance Requirements:** Navigating the evolving regulatory landscape and ensuring compliance with data privacy and security regulations are critical considerations for the pharmaceutical sector.

3) Cost and Implementation Barriers: The initial investment costs associated with implementing blockchain-based cold chain solutions can be substantial [68].

TABLE VIII
COMPARISON OF BLOCKCHAIN ARCHITECTURES/PLATFORMS FOR PHARMACEUTICAL COLD CHAIN

Blockchain Architecture/Platform	**Type**	**Key Features Relevant to Cold Chain**	**Reported Strengths in Pharmaceutical Applications**	**Reported Weaknesses/Challenges in Pharmaceutical Applications**
Hyperledger Fabric	Permissioned	Permissioned access, Channels for data privacy, Modular design, Supports various consensus mechanisms	Strong privacy and control, Suitable for enterprise-level applications with regulatory requirements	Can be complex to set up and manage, May require specific technical expertise
Hyperledger Besu	Permissioned	Ethereum-compatible, Supports private and public transaction processing, EVM for smart contracts, On-chain and off-chain permissioning	Leverages Ethereum ecosystem, Offers flexibility in permissioning	May face similar scalability challenges as public Ethereum without careful design
Ethereum	Public/Private/ Consortium	Smart contracts, Large developer community, High availability, Immutability	Extensive functionality through smart contracts, Transparency in public implementations	Public implementations raise privacy concerns, Scalability can be an issue on the main network, Gas costs can fluctuate
Gcoin Blockchain	Consortium	Consortium Proof-of-Work consensus, Role-based access for participants	Enhances governance and transparency in the drug supply chain	Less widely adopted compared to other platforms, Limited information in the snippets
VeChain Thor	Public Permissioned	Focus on supply chain, Built-in features like multi-party payment and meta-transactions, Proof of Authority consensus	Specifically designed for supply chain traceability and management	Public aspect may raise privacy concerns for some pharmaceutical data
Hyperledger Sawtooth	Permissioned	Modular architecture, Supports various consensus algorithms (including PBFT)	Flexible and scalable for enterprise use	Less prevalent in the reviewed snippets compared to Fabric and Besu
NEM Blockchain	Public/Private	Namespace system for asset management, Uses its own cryptocurrency XEM	Focus on asset tracking and management within the supply chain	Less commonly discussed in the context of pharmaceutical cold chain in these snippets
FISCO BCOS	Consortium	Designed for enterprise use, Focus on regulatory compliance and security	Strong in security and compliance for enterprise applications in certain regions	Limited information available in the provided snippets

- **High Initial Costs:** Costs include platform development, system integration, and hardware/software deployment.
- **Ongoing Operational Costs:** Transaction fees, network maintenance, and specialized technical expertise represent significant barriers [62].
- **Complexity and Learning Curve:** The complexity of implementing these systems and the learning curve associated with blockchain technology further contribute to the challenges faced in widespread adoption.

VI. CONCLUSION

The application of blockchain technology in pharmaceutical cold chain logistics is widely regarded as a promising avenue for enhancing the security, transparency, and efficiency of the supply chain. The reviewed literature consistently highlights blockchain's potential to:

- Significantly improve product traceability across the complex pharmaceutical supply chain.
- Effectively combat the proliferation of counterfeit drugs, a major concern in the pharmaceutical industry.
- Ensure the integrity of temperature monitoring data, which is crucial for maintaining the quality and efficacy of cold chain pharmaceuticals.
- Foster greater trust among stakeholders in the pharmaceutical supply chain by providing transparency and immutability of data.

As indicated in Tables VIII, permissioned blockchain platforms like Hyperledger Fabric and Besu are frequently proposed and appear particularly well-suited for the pharmaceutical industry due to their emphasis on privacy, control, and enterprise-level features. The integration of smart contracts for automation and IoT sensors for real-time environmental data capture are highlighted as key enablers for effective cold chain management.

However, the current research also reveals several challenges and limitations that need to be addressed for widespread adoption :

- **Technical hurdles:** Scalability to handle large volumes of data and transactions and interoperability between different blockchain platforms and existing systems.
- **Organizational and regulatory complexities:** The need for clear regulatory frameworks and addressing data pri-

TABLE IX
TECHNICAL CHALLENGES AND POTENTIAL SOLUTIONS FOR BLOCKCHAIN IN PHARMACEUTICAL COLD CHAIN

Technical Challenge	**Description in Context of Cold Chain**	**Potential Solutions/Future Research Directions**
Scalability	Handling the large volume of temperature data and transactions from a global pharmaceutical supply chain.	Exploring layer-2 scaling solutions, sharding techniques, optimizing consensus mechanisms, utilizing off-chain storage for bulk data.
Interoperability	Integrating blockchain solutions with existing pharmaceutical and logistics systems, as well as different blockchain platforms used by various stakeholders.	Developing standardized data formats and protocols, creating middleware solutions for seamless data exchange, exploring cross-chain communication technologies.
Implementation Costs	High costs associated with setting up the blockchain infrastructure, developing smart contracts, and integrating with hardware and software.	Developing cost-effective blockchain platforms and tools, exploring consortium-based approaches to share infrastructure costs, demonstrating clear return on investment through pilot studies.
Security Vulnerabilities	Potential risks of attacks on blockchain networks and vulnerabilities in smart contracts that could compromise cold chain data.	Implementing robust security protocols, conducting thorough audits of smart contracts, exploring advanced cryptographic techniques, ensuring secure management of private keys.
Lack of Standardized Regulations	Uncertainty due to the evolving legal and regulatory landscape governing the use of blockchain in the pharmaceutical industry.	Engaging with regulatory bodies to establish clear guidelines and standards, developing blockchain solutions that are inherently compliant with existing and emerging regulations.
Data Privacy Concerns	Ensuring the confidentiality and security of sensitive pharmaceutical product and potentially patient data related to cold chain integrity.	Utilizing permissioned blockchain networks with granular access controls, employing encryption techniques for sensitive data, exploring privacy-preserving technologies like zero-knowledge proofs.
Technology Adoption Barriers	Lack of skilled personnel and resistance to adopting new technologies within the pharmaceutical and logistics sectors.	Investing in training and education programs, highlighting the benefits and ease of use of blockchain solutions, providing comprehensive documentation and support.
Blockchain Governance	Establishing clear rules and responsibilities for network participants, managing data access, and resolving disputes within the decentralized network.	Developing robust governance frameworks that define the roles of different stakeholders, establish consensus mechanisms for decision-making, and outline procedures for network management and upgrades.
Big Data Management	Handling the increasing volume of data generated by continuous cold chain monitoring via blockchain and IoT.	Utilizing decentralized storage solutions like IPFS for bulk data, employing Big Data analytics and AI/ML techniques to process and extract insights from the data, optimizing data storage and retrieval strategies.
Integration with Cold Chain Monitoring Technologies	Ensuring the integrity of data from temperature sensors and handling intermittent network connectivity during transportation.	Implementing secure data transmission protocols, developing mechanisms for secure off-chain storage and synchronization of data during connectivity loss, using trusted hardware and secure communication channels for sensor data.

vacy concerns.

- **Cost and implementation barriers:** The expenses associated with deploying and maintaining blockchain solutions.

While numerous theoretical frameworks and simulated implementations have been proposed , the literature suggests a need for more real-world case studies and empirical validation to fully ascertain the practical benefits of blockchain in this domain.

Overall, blockchain technology presents a compelling solution to many of the challenges inherent in pharmaceutical cold chain logistics. Continued research and development, alongside collaborative efforts involving industry stakeholders and regulatory bodies, will be crucial to overcome the existing limitations and fully leverage the transformative potential of blockchain in ensuring a safe, secure, and efficient supply chain for temperature-sensitive pharmaceutical products.

VII. FUTURE WORK

Drawing upon the gaps and limitations identified in the literature, several potential areas for future research warrant further investigation to advance the application of blockchain technology in pharmaceutical cold chain logistics:

A. Enhancing Scalability and Interoperability

Given that scalability and interoperability are significant technical hurdles , future research should prioritize developing more scalable blockchain solutions capable of handling the high transaction volumes in global supply chains. Additionally, investigating innovative approaches to enhance interoperability between diverse blockchain platforms and with existing legacy systems, as suggested by several authors , is crucial for seamless data exchange across the pharmaceutical ecosystem.

B. Real-World Validation and Impact Assessment

As highlighted in Tables II-VI, a significant portion of the current literature focuses on conceptual or prototype-based solutions. Therefore, more real-world case studies and pilot projects are needed to evaluate the practical feasibility and impact of blockchain solutions in pharmaceutical cold chain logistics. These studies should aim to measure tangible benefits and identify unforeseen challenges in real-world deployments.

C. Integration with Emerging Technologies

Future research should increasingly focus on the integration of blockchain with other emerging technologies. As suggested by several papers , the combination of blockchain with Artificial Intelligence (AI) and machine learning could lead to intelligent systems for optimizing logistics and inventory management in the pharmaceutical cold chain. The integration with IoT devices for real-time monitoring of temperature and other critical parameters also presents a significant area for future work.

D. Addressing Regulatory and Governance Challenges

Given the highly regulated nature of the pharmaceutical industry, future research must focus on addressing the regulatory and governance challenges associated with blockchain adoption. Exploring potential frameworks for regulatory compliance, data privacy, and the establishment of industry-wide standards, as suggested by several authors , is critical for facilitating the widespread adoption of blockchain technology.

E. Optimizing Consensus Mechanisms

Further research into optimizing consensus mechanisms for pharmaceutical cold chain applications, considering factors such as security, efficiency, and energy consumption, could lead to more tailored and sustainable blockchain solutions. Exploring alternatives beyond traditional Proof-of-Work and Proof-of-Stake could be beneficial.

F. Economic Implications and Cost-Benefit Analysis

Finally, as highlighted in Table IX, conducting thorough cost-benefit analyses of implementing blockchain solutions in pharmaceutical cold chain logistics is essential. This will provide a clearer understanding of the economic implications and aid organizations in making informed decisions regarding the adoption of this technology.

By focusing on these areas, future research can significantly contribute to overcoming the existing limitations and unlocking the full potential of blockchain technology in ensuring a secure, efficient, and reliable cold chain for pharmaceutical products, ultimately benefiting patient safety and public health.

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