A Robust Drug Recall Supply Chain Management System using Hyperledger Blockchain Ecosystem

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Abstract: Drug recall is a critical issue for manufacturing companies, as a manufacturer might face criticism and severe business downfall due to a defective drug. A defective drug is a highly detrimental issue, as it can cost several lives. Therefore, recalling the drug becomes one of the most sensitive issues in the pharmaceutical industry. This paper presents a blockchain-enabled network that allows manufacturers to effectively monitor a drug while in the supply chain with improved security and transparency throughout the process. The study also tries to minimize the cost and time sustained by the manufacturing company to transfer the drug to the end-user by proposing forward and backward supply chain mathematical models. Specifically, the forward chain model supports drug delivery from the manufacturer to the end-user in less time with a reliable transport mode. The backward supply chain model explicitly focuses on reducing the extra time and cost incurred to the manufacturer in pursuit of recalling the defective drug. Moreover, a real-time implementation of the proposed blockchain-enabled supply chain management system using the Hyperledger Composer is done to demonstrate the transparency of the process.

Keywords: Product Recall, Pharmaceutical Industry, Supply Chain, Blockchain, Hyperledger Composer.

1. Introduction

Blockchain is a distributed ledger technology that is decentralized, unlike existing relational databases, which means each participant is connected to other participants with no governing authority. The data or transactions are stored in blocks that are time-stamped and contain an address of the previous block, such that data cannot be altered. When a miner adds a new block, it is reflected in the entire blockchain network [1]. In the blockchain, a "smart contract," introduced in 1997, is defined as a computer program that can execute any transaction among peers when predefined conditions are satisfied [2]. The smart contract is executed without third-party intervention and helps in paperless transactions and automated logs [2], [3]. A consensus algorithm is a protocol for joint agreement between all parties/nodes within the network on the present state of the ledger. Many consensus algorithms have already been developed, such as Proof of Work (PoW), Proof of Stake (PoS), Proof of Capacity (PoC), and many more [4]–[8].

Based on the participants of the network, blockchain networks can be classified into three different types: (i) public, (ii) private, and (iii) consortium. Anyone can join the network in a public blockchain, but accessing the data is time-consuming [9]. Many advanced schemes have been proposed to reduce this access time in the public blockchain network[10]. In a private blockchain, a single authority or trusted third party acts as a central authority in the network, i.e., the network is centralized by the members of that single organization and no one from outside the organization. Thus this type of blockchain indirectly becomes a centralized network. A consortium blockchain is a semi-private blockchain network where a single organization is not the central authority in the network; instead, a consortium of like-minded organizations forms the authority in the network, which provides decentralization in a network similar to a private blockchain.

During its infancy, blockchain technology was used only for cryptocurrencies [11]. However, nowadays, blockchain technology is applied in various domains, such as healthcare [12], voting systems, anti-money laundering systems, original content creation, secure data, secure multimedia, secure healthcare applications [13]–[20]. In particular, the application of blockchain technology has become very popular in supply chain management, and numerous startups have already been developed for coffee, diamond, and seafood supply chains, among many others. As a concerning issue, the pharmaceutical sector consistently deals with companies that produce fake drugs that can, unfortunately, be fatal. The existence of fake drugs in the pharmaceutical sector is possible only due to an obscure supply chain management, which results in deficiency or surplus availability of drugs. While many solutions have been proposed to improve consumer visibility and automation in the pharmaceutical supply chain [21], [22], the product recall problem remains unsolved in the current supply chain management. Product recall is the process of recollecting defective goods (whether a batch or whole production) from the supply chain hierarchy when there is a manufacturing defect, incorrect labeling, safety issues, or the product has exceeded its shelf life. Product recall is divided into three classes. The most critical is class one, which contains drugs that can cause severe health effects and eventually lead to death. Class two contains drugs that have a possibility of causing severe health effects but are not lethal. Class three is for milder drugs that are not likely to cause severe health issues but could replace drugs for treating a disease [23]. Drug recalls generally increase expenses because the companies have to replace the products and pay for the losses incurred by the consumers [24]. This incurs loss for the manufacturer due to reimbursement for recalled products and unavailability of the drug for the consumer. Currently, pharmaceutical companies use Radio Frequency Identification (RFID) to tag drugs [25] that may cause issues in the market. However, RFID tags have high implementation costs [26] and require complex procedures [27]–[29]. Moreover, the current recall strategies in the traditional supply chain system are tremendously time-consuming due to the obscure nature of the system.

This work proposes a blockchain-enabled supply chain as a novel solution to effectively manage both the forward and backward supply chain. The forward chain works integrate blockchain with the traditional forward chain for drug supply, and the backward chain focuses on the supply chain management in case of a drug recall. In the proposed supply chain, every entity keeps data in their private data store, then the hash of this data is stored as a transaction in the blockchain network. Each transaction is time-stamped and linked so that all transactions are immutable, which supports a secure and transparent supply chain. The significant contributions of this paper include:

- A transparent and autonomous pharmaceutical supply chain management system is proposed, including a product recall by using blockchain technology.
- In the proposed model, the time and cost of supplying drugs to the end-user are minimized for the manufacturing company.
- A real-time implementation of the proposed scheme is presented using the Hyperledger Composer to show the efficiency of the proposed model.

The rest of the paper is divided accordingly. Section 2 discusses the preliminary studies. Section 3 describes the proposed scheme in detail. Section 4 presents the results and discussions of the proposed scheme. Finally, Section 5 concludes this paper and suggests potential research areas for applying the proposed scheme.

2. Preliminary Studies

This section explores the literature on solving problems in the healthcare and pharmaceutical sectors using blockchain. Further, it explains the problems and current solutions in the pharmaceutical and supply chain industries.

2.1 Literature Review

Recent advances in blockchain technology have allowed researchers to use this decentralized system in almost every domain, not only cryptocurrencies. One such beneficial use of the blockchain is in the healthcare and pharmaceutical industries. Healthcare companies move forward with the advancing technology from collecting and analyzing patient data to offering personalized services. However, until recently, these industries had not seen much as to what blockchain technologies can do. Numerous researches in the past decade have allowed blockchain to integrate with other technologies to offer highly technical services to patients. One such study by Abdellatif et al. [30] combines edge computing and blockchain to discover probable epidemics, remote monitoring of patients, and fast responding services. Further, it provides a secure method to remotely share and access medical data among the stakeholder healthcare entities.

Hastig and Sodhi [31] have used the same blockchain network for the supply chain traceability of two contrasting domains - cobalt mining and pharmaceutical. The proposed blockchain solution can handle different business requirements dynamically. However, some of the business requirements remain the same across different industries, like analyzing market trends, improving sustainability, increasing operational efficiency, stopping illegal industrial practices, and improving supply chain operability. The tracking system proposed would flag the cobalt from suspicious mines. This suspicion is indicated because the particular mine produces a certain amount of metal. If it exceeds that amount, it indicates mineral mixing. Similarly, the model could be used to identify false drugs in the supply chain.

Mattke et al. [32] have also discussed a blockchain solution, "MediLedger", to identify counterfeit drugs as an enterprise solution. The study proposes using "benevolent dictator," which means that a "kind" central authority can manage the blockchain on behalf of the pharmaceutical company as it could be a liability to them. To address the scalability issues, they suggest storing the verification of the transaction rather than the transactions themselves. It also uses a zero-knowledge algorithm to cater to the data privacy of the users. The algorithm was used initially in the Zerocash cryptocurrency to protect the identity of the payer, the payee, and the amount paid [33]. The algorithm allows users to store the sensitive transaction data to their private node and verify the transaction on the public ledger so that the other users can verify the transaction's sanity without actually decoding the transaction.

Stafford and Treiblmaier [34] have emphasized the need to securely store the medical and health records of the patients by proposing a blockchain-based network to store such records securely. The study uses a ground-theory approach to develop a blockchain system and concludes with a qualitative analysis of electronic records from the United States of America's patients. The interviews were based on the ground theory approach meaning the first interview might point out to some other relevant interviewee and build a chain of subsequent comparative interview analyses.

Alketbi et al. [35] have devised a blockchain solution for investigative analysis of pharmaceutical drug recall. The study includes a stage of Out-of-Specification (OOS) and Out-of-Trend (OOT) analysis for the recalled drugs. As the name suggests, these investigation stages lookout for any specification that the drug was missing from the original thought idea. If any other drug salt is curing, the same problem has overtaken the existing drug salt usage trend, respectively. The study also incorporates quality issues detection, which includes an intensive analysis in the lab, including testing the batch and its raw materials, comparing the batch to the previous batches to identify OOS samples, etc.

Alketbi et al. [36] have tried to explore the applications of blockchain for the government sector. The government of Dubai has set up a Global Blockchain Council, a public-private partnership entity that allows the government to partner with private companies to develop blockchain solutions. One such application of the council is the Emirates Integrated Telecommunication Corporation. Similarly, the government of the UK approved a fin-tech startup company to support the government with blockchain solutions, and later in 2018, approved Blockchain-as-a-Solution (BaaS). One of the most popular techniques used prior to blockchain for securing the pharmaceutical supply chain is called Auto-ID developed at the Massachusetts Institute of Technology (MIT) [37]. This technology provides two most needed dimensions for supply chain security, i.e. instant verification of any drug at any location and a robust track-and-trace system. This is achieved primarily through the use of RFID tags backed with Electronic Product Code (EPC). Auto-ID technology uses EPC as a pointer for drug information stored in a remote database, which is much more efficient than bar codes that do not allow remote information retrieval. Each unique EPC further had a corresponding file written in Physical Markup Language (PML) and saved in a different PML server. Finally, to map the EPC to a named drug Object Name Service (ONS) based on Domain Name System (DNS) is used.

Sylim et al. [38] have developed a Distributed App to detect fake and/or below-the-standard drugs in the distribution network. The developed blockchain network uses five nodes: i) the Food and Drug Administration (FDA), ii) manufacturer, iii) wholesaler, iv) retailer, and v) consumer. The network runs on the Swarm distributed file system. There are two prototypes in Ethereum and Hyperledger Fabric in this scheme, and further proposes to use Delegated Proof of Service (DPoS) or Practical Byzantine Fault Tolerance (PBFT) consensus mechanism in the Ethereum network instead of the currently used PoW because of their excellent scaling capacity.

Dwivedi et al. [39] have developed a logic for smart contract and consensus mechanism specific to the pharmaceutical supply chain. The directed graph-based architecture of the smart contract includes six states and six actions. States 0 to 4 represent the supply chain stakeholders like manufacturer, warehouse, retailer, pharmacist and end-user. State 5 represents a dead state. The actions include purchase, supply, demand, delivery, no action and violation. This scheme also performs key management in smart contracts, making the system robust against security attacks.

Tseng et al. [40] have proposed the use of the G-Coin blockchain network for drug supply chains. This is a digital gold currency based on blockchain technology and is robust specifically against the “double-spend” attack. Double spending refers to using the same resources already being used to mine a block in the blockchain, thus allowing the attacker to “double-spend” their resources. In addition, the authors have used the PoW consensus mechanism along with the G-Coin architecture. They have also proposed a continuous surveillance model instead of the traditional “inspect-and-examine” model for counterfeit drug supply.

Table 1 shows the analysis of the existing survey that reveals the major problems faced by the healthcare and pharmaceutical industries. However, there lacked some studies on the product recall issues from the manufacturer's perspective. Drug recall should not always be thought of as a negative for the manufacturer. Sometimes, the manufacturers recall back the drug for quality improvement even though it might not be lethal, incurring the cost for the sake of better quality products. This can sometimes have a positive impact on the company's reputation [24]. So, there is a need for an effective solution that can help manufacturers reduce their costs and increase their reliability. While being able to curb supply chain malpractices, which often go unnoticed as assumed by the company, they incur the loss.

Table 1: Theoretical analysis of the existing literature

Study	Domain	Technique Used	Description
Abdellatif et. al. [30]	Healthcare	A combination of restricted-fully restricted blockchain with edge computing	Discovering probable epidemics, remotely monitoring patients and fast responding service. Provides a secure method to remotely share and access the medical data among the stakeholder healthcare entities.
Hastig and Sodhi [31]	Cobalt mining and pharmaceutical supply chain	Consortium blockchain	Proposes traceability in different industry supply chains based on some business-critical factors which are the same across different domains.
Mattke et. al. [32]	United States pharmaceutical supply chain	Private permissioned blockchain with proof of authority consensus mechanism	Uses the concept of "benevolent dictator", i.e. a "kind" central authority that manages the blockchain on behalf of the pharmaceutical company. Addresses scalability issues by storing the verification of the transaction rather than the transactions.
Stafford and Treiblmaier [34]	Medical Data Storage	Consortium blockchain	The study uses a ground-theory approach to develop a blockchain system and concludes with qualitative analysis on the electronic records from the United States of America's patients.
Wu and Lin [35]	Pharmaceutical Recall	Consortium blockchain based on component-based smart contract	Performs an investigative analysis of the pharmaceutical drug recall. The study includes a stage of Out-of-Specification (OOS) and Out-of-Trend (OOT) analysis for the recalled drugs.
Alketbi et. al. [36]	Government Sectors	Blockhain-as-a-Service model	Studies current blockchain solutions implemented in the government sectors.
Sylim et. al. [38]	Pharmaceutical Supply Chain	Distributed App based on Ethereum and Hyperledger Fabric with DPoS or PBFT consensus mechanism	Develops two instances of blockchain in Ethereum and Hyperledger Fabric with DPoS or PBFT as the consensus mechanism among the nodes. The nodes include the FDA of the US, manufacturer, wholesaler, retailer and consumer.
Dwivedi et. al. [39]	Pharmaceutical Supply Chain	Directed graph-based architecture for smart contracts	Develops a smart contract algorithm based on directed graphs with six states and six actions. It Performs strong key management in smart contracts, making the system robust against security attacks.
Tseng et. al. [40]	Pharmaceutical Supply Chain	G-coin blockchain architecture	Makes use of the G-coin blockchain architecture to provide robustness against “double-spend” problem in drug market, which uses PoW as consensus mechanism.

Through the mathematical models developed in this study, the manufacturers can estimate the costs and time that the whole supply chain is going to take and store them in their private ledger hidden from the rest of the stakeholders in the supply chain. Finally, once a supply chain cycle finishes, the manufacturer can have a “robust” auditing strategy for the cost and time efforts made versus the outstanding efforts that should have been made.

2.2 Pharmaceutical Industry: Problems and Current Solutions

A new drug takes around 8-10 years of research and testing before it is available to the public. While the time commitment of later stages, such as pre-clinical research and clinical trials, can be reduced in the face of a pandemic like COVID-19 [41], the time required for a preliminary study varies unprecedently. A typical drug lifecycle is shown in Figure 1, in which the initial stage, i.e., drug study, is marked in blue. Pre-clinical research involves verifying the toxicity level of the drug under consideration and an animal testing stage. A clinical trial consists of three phases that a drug must go through before becoming available to the market. Then monitoring phase is performed to analyze the drug's consequences after releasing it to the public.

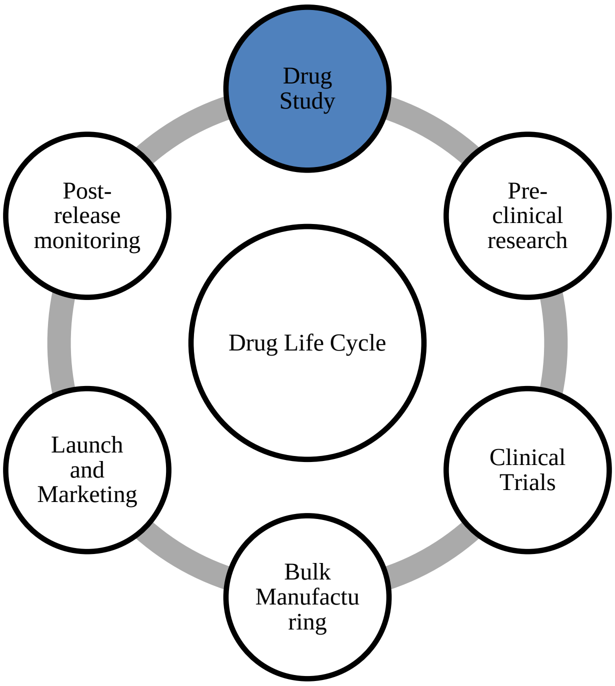


Figure 1: Drug life cycle

Effect of the socio-economic factors also poses a challenge as the healthcare costs are likely to increase with an increase in populations. Reasons for drug failure include the preliminary design of the storage and manufacturing areas and poor survival potential of the microorganisms from a microbiological perspective [42]. The continuous outbreak of new viruses, such as SARS CoV-2 (popularly known as COVID-19) (2019), Ebola (2014), Rotavirus (2008), and Marburg Virus (2000), have forced the pharmaceutical sector to upgrade its supply chain system to improve the reachability and visibility of drugs for treatment to end-users.

2.3 Supply Chain Management

The supply chain is a complex network of numerous stakeholders responsible for supplying the market with products that consumers later expend. Such stakeholders, including manufacturers, warehouse units, distribution centers, logistics, and pharmacies, work together directly or indirectly to obtain and process the raw materials and ship the processed material to consumers [43]. This system can also be termed the management of inter-business chains [44]. A supply chain responsible for supplying consumers exists for all types of products, from food, pharmaceutical, and textile supply chains to construction, chemical, and any other Fast Moving Consumer Goods (FMCG) supply chains.

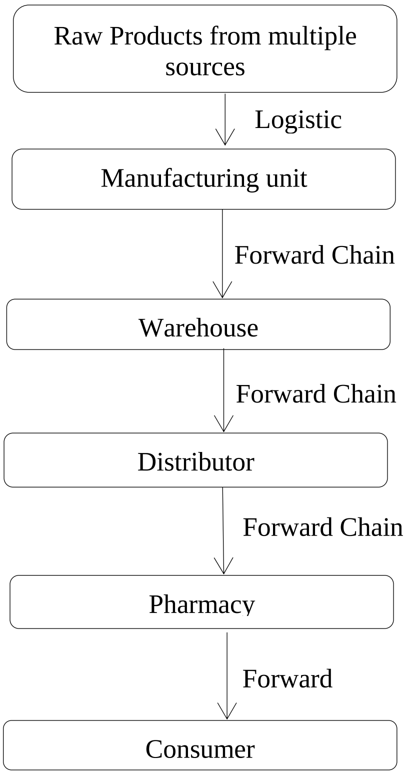


Figure 2: Traditional supply chain

Figure 2 illustrates the process involved in a traditional supply chain. Several processes, including the flow, must be optimized in a supply chain, such as reducing the total cost of making the product, minimizing the product's delivery time, and maximizing the reliability of the logistics at the same time [45]. In the vehicle routing problem, vehicles are responsible for meeting the global market demands following the optimal route, i.e., low cost and high reliability [46]. Since vehicles perform both the delivery and collection of the product, the problem is if a vehicle travels on more than one route. The main aim of the problem is to determine a minimal travel distance while fulfilling the market needs. Another constrain is that consumer demand is never static and consistently changes with time [46]. Numerous other problems lead to delayed processes in the supply chain and eventually deteriorate the industry's backbone. Therefore, a blockchain-enabled supply chain has been developed to solve these issues, as discussed in the next section.

3. Proposed Work

A novel drug supply chain management system based on blockchain technology is proposed in this paper considering the product recall problem. The proposed drug supply chain assumed that there are enough distributors in an area. So, cargo ships, airplanes and trains are not required to deliver drugs from distributors to the pharmacies. However, delivery trucks are enough to distribute the drugs. The proposed work entertains the stakeholders within a country only. Cross-border trades are not considered here. Third-party warehouses are not considered and assumed that manufacturers store all the products in their own warehouses. Two mathematical models have also been proposed that enable a manufacturer to calculate overall costs, time efforts, and the reliability of their transportation modes on different routes for both the forward and backward chains. The mathematics is stored privately by the manufacturer in its private copy of the ledger. In case of a probable fraud, the transactions from the mathematical models and the transactions performed in the blockchain can be compared, allowing the manufacturer to trace the defaulter easily. The requirements of the presented method are given below:

- One of the prime requirements of this study is that all the stakeholders need to migrate to the blockchain-based ERP systems from the currently used traditional centralized ERP systems, which are managed individually at the stakeholder level.
- The blockchain environment requires network consensus for every step, which needs dedicated systems with high-end hardware components. It must support a quick resolution in case of a recall.
- The developed blockchain model is a prototype, where a single node for every category of entity is created by the admin node, i.e. manufacturer (in this case). However, there can be multiple nodes for every stakeholder category. They can customize the access permissions for the blockchain network with the admin to control all the activities.

3.1 Pharmaceutical Sector Supply Chain

A framework for a sustainable supply chain must include a method to identify the most suitable supplier, manufacturing, and warehousing sites and evaluate the environmental and economic impact of different supply chain designs [47].

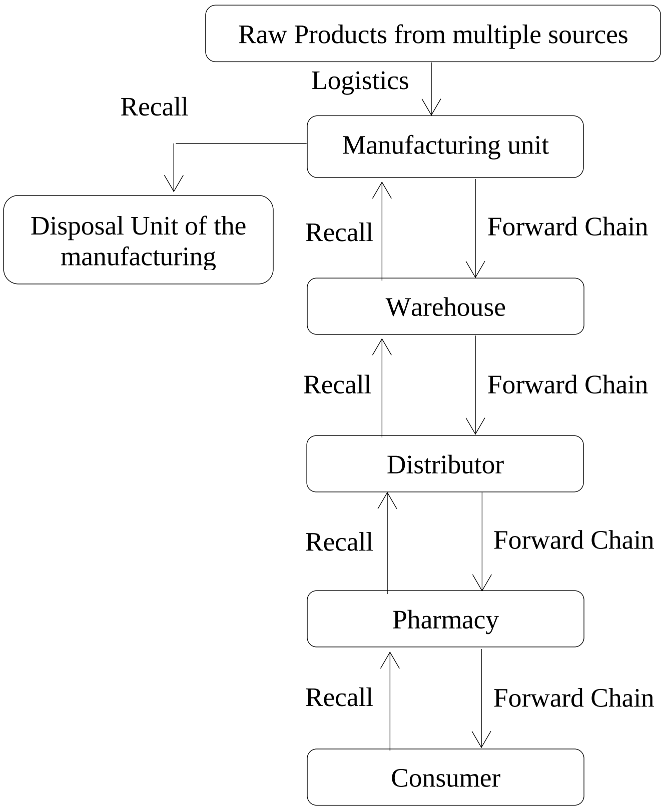


Figure 3: Proposed supply chain with a product recall for the pharmaceutical sector

The proposed transparent pharmaceutical supply chain, including the product recall phase, is shown in Figure 3. The illustrated supply chain includes both forward and backward supply chains. The forward chain works in its regular fashion with the change of ownership until it reaches the consumer, then transitions to the recall procedure. Specific steps and procedures must be followed when there is a possibility of recall. For instance, if a defective drug is recognized, the recall procedure is initiated to return the corresponding drug to the manufacturer. In this process, the manufacturer checks its database to determine the number of defective drugs available on the market then commences the recall process. The distributor collects the defective drugs from the pharmacy and forwards them to the manufacturer through the warehouse. Once all defective drugs are returned to the manufacturer, the procedure ends [23]. The proposed supply chain implements a blockchain network to maintain transparency, whereby blockchain supports the forward and backward chains to increase the manufacturer's control over the drugs. Each entity, i.e., Manufacturer, Warehouse, Distributor, and Pharmacist, is a blockchain network member, which maintains a record for each unit of the drug.

Figure 4 presents the application of blockchain in the pharmaceutical supply chain paradigm. Every participant in the network maintains their own set of local databases that contain information about the drug and its relation to the organization. Hashes of all data are stored locally in the blockchain for two purposes: (i) to improve privacy and (ii) to tackle the scalability issues [48]. Hashing can be done with different algorithms, such as Message Digest 5 (MD5) [49], Secure Hash Algorithm (SHA) [50] family of hashing algorithms, New Technology LAN Manager (NTLM) algorithm [51], DNA based encryption [52], attribute-based encryption [53], among others. This presented work uses SHA256 [54] as a hashing algorithm in the network. A blockchain network is maintained to store all the transactions, including the hashes. This enables all entities of the network to verify the concerned transaction's hash following the previous hash to visualize the current status of the process without seeing the actual transaction.

Each participant in the supply chain maintains their own data storage ledger with complete information about the products and transactions. A raw product supplier stores the amount of product delivered to the manufacturer, the quantity ordered, quantity recalled if any, cost per unit product, transportation, and all other costs involved in the exchange process. Similarly, the manufacturer stores the quantity they delivered, the quantity they received, quantity recovered due to recall or lost during transportation, different costs involved, product expiration, and quantity ordered by the warehouse. Warehouses, distributors, and pharmacies perform a similar mechanism to maintain their own sets of databases or ledgers that is not visible to others involved in the blockchain; only the relevant information is shown on demand. In addition to this, the manufacturer stores the total costs, time commitments, and the reliability factor of their transport calculated using the mathematical models in its private data storage. This is done so that the manufacturer doesn't incur unnecessary costs and delays in a compromised network. Every company conducts internal and external auditing sessions half-yearly or yearly, where these metrics are made as a base and the actual incurred costs and time efforts are analyzed. Since every transaction in the supply chain is stored publically over the blockchain, the manufacturer, on its level, compares the statistics and quickly finds out the defaulter without him knowing as the audit data is kept private.

3.2 Forward and Backward Supply Chain Management

Herein, two mathematical models are proposed for the forward supply chain and backward supply chain to develop a blockchain network focusing on product recall. It was assumed that all participating entities are within the same country, so only a domestic manufacturing unit, its warehouse(s), distributors, and pharmacies are considered. In the forward supply chain, the manufacturer develops a specialty drug in its manufacturing unit, then the batches of that drug reach the warehouses via different modes of transport. Then, the drug moves from the warehouses to different distributors who have ordered that specialty drug. Since the distributors may be located far from the warehouse, cargo planes are used as the transportation mode for this exchange of drugs, which are much more feasible than delivery by trucks better for shorter distances. The next stage of transfer is from the distributors to the pharmacies (independent and hospital pharmacies are considered as a single entity in this study). For this exchange, delivery trucks are used as the mode of transportation because it is assumed that there are enough pharmacies within a city, in other words, within shorter distances, as mentioned above. In the case of a product recall, the manufacturing company is responsible for recollecting all the faulty batches of the drug. This process is initiated by invoking a message publically that the manufacturer M has decided to recall drug d with batch no. b. After the pharmacies, distributors, and warehouses identify the corresponding stock in their inventories, a contract order is placed with sellers who have that particular batch and need it to be recalled. The seller verifies this claim in their inventory and initiates the recall mechanism by clearing out the inventory and reimbursing the buyers. This process is repeated until the manufacturer has received all defective drugs from the warehouses. Ultimately, the manufacturer decides what to do with the recalled product once the process is completed. The whole process is explained mathematically using various notations explained across Tables 2-8.

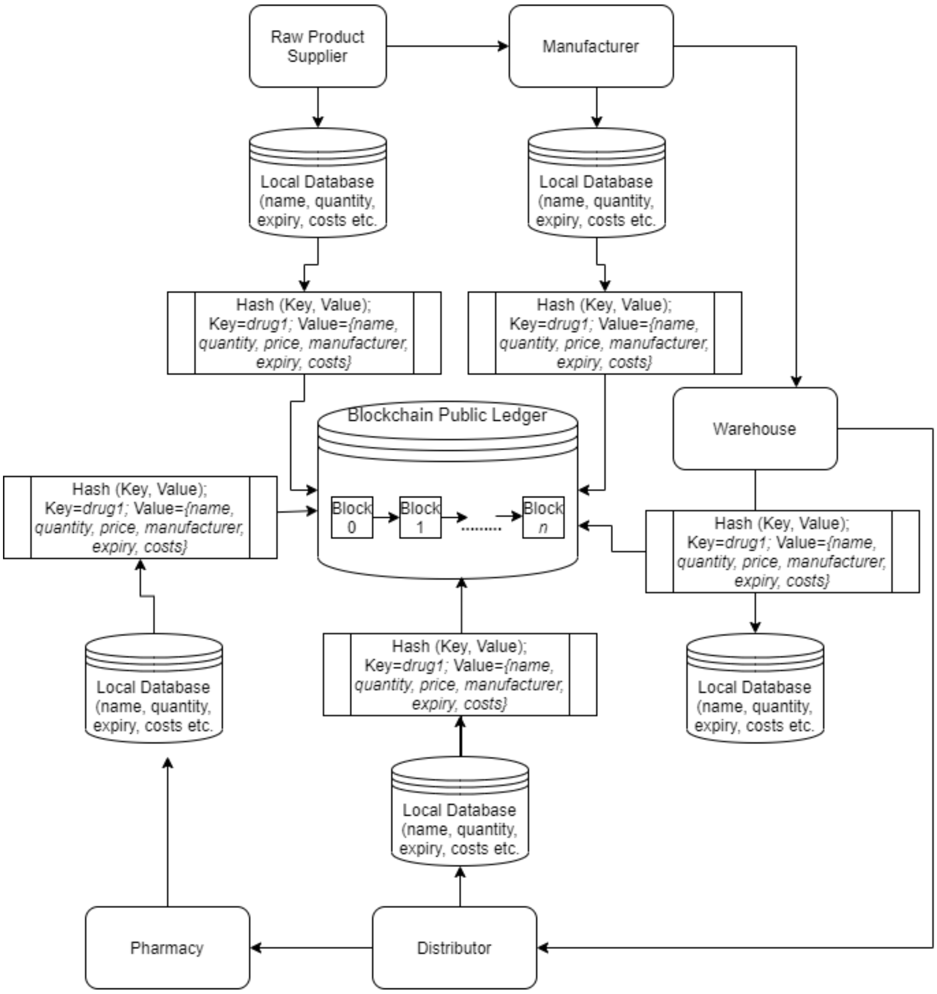


Figure 4: Supply chain using blockchain technology

Let M be the set of a manufacturing unit, W the set of warehouses, D the set of distributors, P the set of pharmacies, t be specific time point, d the drug under consideration, T_T the transport type by Truck, T_A the transport type by cargo airplane, r the set of routes in a forward chain and r' the set of routes in the backward chain for the subsequent work.

Multiple costs are involved in the whole network, which ensures the flow of a product from one level to another in the supply chain. These costs are crucial for the manufacturer to have an idea of what value they are losing from the recall to develop business strategies accordingly for the future.

Table 2: Parameters involved in ordering cost and inventory cost

Notations	Descriptions
$OC_{MW}^{t}, OC_{WD}^{t}, OC_{DP}^{t}$	Ordering cost from one level to another at time t.
OQ_{WMd}^{t}	Order quantity of drug d by warehouse W to manufacturing unit M at time t.
OQ_{DWd}^{t}	Order quantity of drug d by distributor D to warehouse W at time t.
OQ_{PDd}^{t}	Order quantity of drug d by pharmacy P to distributor D at time t.
IC_{Md}^{t}	Inventory holding cost of drug d at manufacturing unit M at time t.
IC_{Wd}^{t}	Inventory holding cost of drug d at warehouse W at time t.
IC_{Dd}^{t}	Inventory holding cost of drug d at distributor D at time t.
IC_{Pd}^{t}	Inventory holding cost of drug d at pharmacy P at time t.
$CS_{dM}^{t}, CS_{dW}^{t}, CS_{dD}^{t}, CS_{dP}^{t}$	The current stock of drug d available at the manufacturing unit, warehouse, distributor, and pharmacy, respectively.

Total ordering costs in the network =

$$\sum_{M}\sum_{W}\sum_{t}(OC_{MW}^{t}\ .\ OQ_{WMd}^{t}) + \sum_{W}\sum_{D}\sum_{t}(OC_{WD}^{t}\ .\ OQ_{DWd}^{t}) + \sum_{D}\sum_{P}\sum_{t}(OC_{DP}^{t}\ .\ OQ_{PDd}^{t}) \tag{1}$$

Since there are multiple manufacturers, warehouses, distributors, and pharmacies, the costs from all these entities are added. The total ordering cost is calculated by multiplying other factors as shown in Eq. (1) using parameters from Table 2.

Total inventory cost in the network =

$$\sum_{M}\sum_{t}(IC_{Md}^{t}\ .\ CS_{dM}^{t}) + \sum_{W}\sum_{t}(IC_{Wd}^{t}\ .\ CS_{dW}^{t}) + \sum_{D}\sum_{t}(IC_{Dd}^{t}\ .\ CS_{dD}^{t}) + \sum_{P}\sum_{t}(IC_{Pd}^{t}\ .\ CS_{dP}^{t}) \tag{2}$$

The inventory cost of a unit quantity of drug and the current stock of the drug are multiplied, and then all the values are added to calculate the total inventory cost as shown in Eq. (2) using parameters from Table 2.

Table 3: Parameters involved in fixed cost, production cost and back-ordering cost

Notations	Descriptions
$FC_{M}^{t}, FC_{W}^{t}, FC_{D}^{t}, FC_{P}^{t}$	Fixed cost involved in Manufacturing unit, Warehouse, Distributors and Pharmacy at time t (includes salaries of employees, interest on loans, etc).
PC_{dM}^{t}	Production cost of drug d at the manufacturing unit M at time t.
BOC_{Md}^{t}	Back Order cost for drug d at the manufacturing unit M at time t.
BQ_{Md}^{t}	Backorder quantity of drug d at manufacturing unit M at time t.

$$\text{Total fixed cost in the network } = \sum_{M}\sum_{t} FC_{M}^{t} + \sum_{W}\sum_{t} FC_{W}^{t} + \sum_{D}\sum_{t} FC_{D}^{t} + \sum_{P}\sum_{t} FC_{P}^{t} \tag{3}$$

In Eq. (3), the total fixed cost includes the fixed costs and that is to be sustained by the bearer. This cost can be the cost of electricity, water, corporate bills, and paying salaries to the employees using the parameters listed in Table 3.

$$\text{Production cost } = \sum_{M}\sum_{t} PC_{dM}^{t} \tag{4}$$

The production cost is the cost of producing the drug d for the manufacturer, which is shown in Eq. (4), also calculated using the parameters from Table 3.

$$\text{Back ordering cost } = \sum_{M}\sum_{t}(BOC_{Md}^{t}\ .\ BQ_{Md}^{t}) \tag{5}$$

Backorder cost in Eq. (5) refers to the cost of the quantity of the drug that the buyer rejects due to quality issues. This can be calculated by multiplying the unit quantity back-ordering cost and the total back-ordered quantity. These parameters are also listed in Table 3.

Table 4: Parameters involved in delivery and purchasing cost

Notations	**Descriptions**
DC_{MWd}^{t}	Delivery cost of drug d from manufacturer M to warehouse W at time t.
DC_{WDd}^{t}	Delivery cost of drug d from warehouse W to distributor D at time t.
DC_{DPd}^{t}	Delivery cost of drug d from distributor D to pharmacy P at time t.
DQ_{MWd}^{t}	Delivered quantity of drug d by manufacturing unit M to warehouse W at time t.
DQ_{WDd}^{t}	Delivered quantity of drug d by warehouse W to distributor D at time t.
DQ_{DPd}^{t}	Delivered quantity of drug d by distributor D to pharmacy P at time t.
$PurC_{MWd}^{t}$	Purchasing cost of drug d from manufacturer M to warehouse W at time t.
$PurC_{WDd}^{t}$	Purchasing cost of drug d from warehouse W to distributor D at time t.
$PurC_{DPd}^{t}$	Purchasing cost of drug d from Distributor D to pharmacy P at time t.
$PurQ_{WMd}^{t}$	A purchased quantity of drug d by warehouse W from manufacturing unit M at time t.
$PurQ_{DWd}^{t}$	A purchased quantity of drug d by distributor D from warehouse W at time t.
$PurQ_{PDd}^{t}$	A purchased quantity of drug d by pharmacy P from distributor D at time t.

$$\begin{aligned}&\text{Total delivery cost in the network}\\ &= \sum_{M}\sum_{W}\sum_{t}(DC_{MWd}^{t}\ .\ DQ_{MWd}^{t})\\ &+ \sum_{W}\sum_{D}\sum_{t}(DC_{WDd}^{t}\ .\ DQ_{WDd}^{t}) + \sum_{D}\sum_{P}\sum_{t}(DC_{DPd}^{t}\ .\ DQ_{DPd}^{t})\end{aligned} \tag{6}$$

The delivery cost in Eq. (6) is calculated by multiplying the delivery cost per unit quantity and the total delivered quantity to the buyer, then these values are added. The parameters are listed in Table 4.

Total purchasing cost in the network =

$$\sum_{M}\sum_{W}\sum_{t}(PurC_{MWd}^{t}\ .\ PurQ_{WMd}^{t}) + \sum_{W}\sum_{D}\sum_{t}(PurC_{WDd}^{t}\ .\ PurQ_{DWd}^{t}) + \sum_{D}\sum_{P}\sum_{t}(PurC_{DPd}^{t}\ .\ PurQ_{PDd}^{t}) \tag{7}$$

The total purchasing cost is calculated in the same way as the delivery cost. Here, the product of purchasing quantity and the purchasing cost per unit quantity of drug is added. This cost is calculated by using Eq. (7) using the parameters from Table 4.

Table 5: Parameters involved in transportation cost and reliability loss

Notations	Descriptions
$\delta_{MW}, \delta_{WD}, \delta_{DP}$	Distance from manufacturing unit M to warehouse W, warehouse W to distributor D and distributor D to pharmacy P respectively.
$\beta_{MWd}^{tT_T}$	Quantity of drug d delivered by transport type T_T from manufacturing unit M to warehouse W at time t.
$\beta_{MWd}^{tT_A}$	Quantity of drug d delivered by transport type T_A from manufacturing unit M to warehouse W at time t.
$\beta_{WDd}^{tT_T}$	Quantity of drug d delivered by transport type T_T from warehouse W to distributor D at time t.
$\beta_{WDd}^{tT_A}$	Quantity of drug d delivered by transport type T_A from warehouse W to distributor D at time t.
$\beta_{DPd}^{tT_T}$	Quantity of drug d delivered by transport type T_T from distributor D to pharmacy P at time t.
$TC_{MWdT_T}^{tr_{MW}}$	Transportation cost of drug d with transport type T_T from manufacturer M to warehouse W on route $r_{MW}\mathrm{r}_{\mathrm{MW}}$ at time t.
$TC_{MWdT_A}^{tr_{MW}}$	Transportation cost of drug d with transport type T_A from manufacturer M to warehouse W on route r_{MW} at time t.
$TC_{WDdT_T}^{tr_{WD}}$	Transportation cost of drug d with transport type T_T from warehouse W to distributor D on route r_{WD} at time t.
$TC_{WDdT_A}^{tr_{WD}}$	Transportation cost of drug d with transport type T_A from warehouse W to distributor D on route r_{WD} at time t.
$TC_{DPdT_T}^{tr_{DP}}$	Transportation cost of drug d with transport type T_T from distributor D to pharmacy P on route r_{DP} at time t.
FC_M^t , FC_W^t , FC_D^t	Fixed cost involved in Manufacturing unit, warehouse, and Distributors at time t (includes salaries of employees, interest on loans, etc).
$\alpha_{T_T}^{r_{MW}}$	Reliability rate of transport T_T on route r_{MW}.
$\alpha_{T_A}^{r_{MW}}$	Reliability rate of transport T_A on route r_{MW}.
$\alpha_{T_T}^{r_{WD}}$	Reliability rate of transport $T_T\mathrm{T}_{\mathrm{T}}$ on route r_{WD}.
$\alpha_{T_A}^{r_{WD}}$	Reliability rate of transport T_A on route r_{WD}.
$\alpha_{T_T}^{r_{DP}}$	Reliability rate of transport T_T on route r_{DP}.

Total Transportation cost in the network =

$$\begin{aligned}
&\sum_{M}\sum_{W}\delta_{MW}\,[(\sum_{M}\sum_{W}\sum_{t}\sum_{T_T}\beta_{MWd}^{tT_T}\cdot\sum_{r_{MW}}TC_{MWdT_T}^{tr_{MW}})\\
&\qquad+(\sum_{M}\sum_{W}\sum_{t}\sum_{T_A}\beta_{MWd}^{tT_A}\cdot\sum_{r_{MW}}TC_{MWdT_A}^{tr_{MW}})]\\
&\qquad+\sum_{W}\sum_{D}\delta_{WD}\,[(\sum_{W}\sum_{D}\sum_{t}\sum_{T_T}\beta_{WDd}^{tT_T}\cdot\sum_{r_{WD}}TC_{WDdT_T}^{tr_{WD}})\\
&\qquad+(\sum_{W}\sum_{D}\sum_{t}\sum_{T_A}\beta_{WDd}^{tT_A}\cdot\sum_{r_{WD}}TC_{WDdT_A}^{tr_{WD}})]+\sum_{D}\sum_{P}\delta_{DP}\,(\sum_{D}\sum_{P}\sum_{t}\sum_{T_T}\beta_{DPd}^{tT_T}\cdot\sum_{r_{DP}}TC_{DPdT_T}^{tr_{DP}})
\end{aligned} \tag{8}$$

Eq. (8) calculates the total transportation cost by multiplying the quantities delivered by different vehicle types and the per-unit transportation cost. The sum of these transportation costs is multiplied by the distance between the buyer and seller units to calculate the total transportation cost. The variables used to calculate this cost are listed in Table 5.

Total reliability loss =

$$\sum_{M}\sum_{W}\delta_{MW}\,[(\sum_{M}\sum_{W}\sum_{t}\sum_{T_T}\beta_{MWd}^{tT_T}\,.\,\alpha_{T_T}^{r_{MW}}\,.\,FC_M^t) \\ +(\sum_{M}\sum_{W}\sum_{t}\sum_{T_A}\beta_{MWd}^{tT_A}\,.\,\alpha_{T_A}^{r_{MW}}\,.\,FC_M^t)\,]+\sum_{W}\sum_{D}\delta_{WD}\,[(\sum_{W}\sum_{D}\sum_{t}\sum_{T_T}\beta_{WDd}^{tT_T}\,.\,\alpha_{T_T}^{r_{MD}}\,.\,FC_W^t) \\ +(\sum_{W}\sum_{D}\sum_{t}\sum_{T_A}\beta_{WDd}^{tT_A}\,.\,\alpha_{T_A}^{r_{MD}}\,.\,FC_W^t)]+\sum_{D}\sum_{P}\delta_{DP}\,(\sum_{D}\sum_{P}\sum_{t}\sum_{T_T}\beta_{DPd}^{tT_T}\,.\,\alpha_{T_T}^{r_{DP}}\,.\,FC_D^t) \tag{9}$$

The reliability loss is calculated by Eq. (9) for the loss incurred due to the lack of reliability of different shipping modes. Suppose that the drug requires a delivery vehicle to have a critical temperature range, but it fails to do so. This is considered a reliability loss and is calculated by summing up the multiplied amount of drug quantity delivered by the particular vehicle type. The reliability factor ranges between 0 and 1 and the fixed cost is involved here. The reliability is calculated using the parameters described in Table 5.

Finally, the total end-to-end cost in the forward chain is the cost involved in a drug reaching from the manufacturer to the pharmacy, which is given in Eq. (10). It is calculated by adding the different costs determined in Eqs. (1) to (9).

The total end-to-end cost in the forward chain =

$$Total\ ordering\ cost\ +\ Total\ inventory\ cost\ +\ Total\ fixed\ costs +\ Total\ \ Production\ cost \\ +\ Total\ Back-ordering\ cost\ +\ Total\ delivery\ cost \\ +\ Total\ Purchasing\ cost +\ Total\ Transportation\ cost \\ + Total\ Reliability\ loss \tag{10}$$

Table 6: Parameters involved in delivery time

Notations	Descriptions
$\tau_{MWr_{MW}}^{T_T}$	Travel time from manufacturing unit M to warehouse W on route r_{MW} with transport T_T.
$\tau_{MWr_{MW}}^{T_A}$	Travel time from manufacturing unit M to warehouse W on route r_{MW} with transport T_A.
$\tau_{WDr_{WD}}^{T_T}$	Travel time from warehouse W to distributor D on route r_{WD} with transport T_T.
$\tau_{WDr_{WD}}^{T_A}$	Travel time from warehouse W to distributor D on route r_{WD} with transport T_A.
$\tau_{DPr_{DP}}^{T_T}$	Travel time from distributor D to pharmacy P on route r_{DP} with transport T_T.
$\beta_{WMd}^{tT_T}$	Quantity of drug d delivered by transport type T_T from warehouse W to manufacturing unit Mat time t.
$\beta_{WMd}^{tT_A}$	Quantity of drug d delivered by transport type T_A from warehouse W to manufacturing unit M at time t.
$\beta_{DWd}^{tT_T}$	Quantity of drug d delivered by transport type T_T from distributor $D$to warehouse W at time t.
$\beta_{DWd}^{tT_A}$	Quantity of drug d delivered by transport type T_A from distributor D to warehouse W at time t.
$\beta_{PDd}^{tT_T}$	Quantity of drug d delivered by transport type T_T from pharmacy P to distributor Dat time t.
χ	A variable ranging between 0 and 1

Total delivery time =

$$\sum_{M}\sum_{W}\sum_{T_T}(\sum_{t}\beta_{MWd}^{tT_T}\cdot\sum_{r_{MW}}\tau_{MWr_{MW}}^{T_T})$$
$$+\sum_{M}\sum_{W}\sum_{T_A}(\sum_{t}\beta_{MWd}^{tT_A}\cdot\sum_{r_{MW}}\tau_{MWr_{MW}}^{T_A})+\sum_{W}\sum_{D}\sum_{T_T}(\sum_{t}\beta_{WDd}^{tT_T}\cdot\sum_{r_{WD}}\tau_{WDr_{WD}}^{T_T})$$
$$+\sum_{W}\sum_{D}\sum_{T_A}(\sum_{t}\beta_{WDd}^{tT_A}\cdot\sum_{r_{WD}}\tau_{WDr_{WD}}^{T_A})+\sum_{D}\sum_{P}\sum_{T_T}(\sum_{t}\beta_{DPd}^{tT_T}\cdot\sum_{r_{DP}}\tau_{DPr_{DP}}^{T_T}) \tag{11}$$

The total time for an end-to-end delivery is given in Eq. (11), which includes the delivery time from the seller to the buyer using different shipment types. This can be calculated by multiplying the quantity of drug delivered by the particular vehicle type and the delivery time that the particular vehicle took using the specified route explained in Table 6.

$$\beta_{MWd}^{tT_T}+\beta_{MWd}^{tT_A}=DQ_{MWd}^{t} \tag{12}$$
$$\beta_{WDd}^{tT_T}+\beta_{WDd}^{tT_A}=DQ_{WDd}^{t} \tag{13}$$
$$\beta_{DPd}^{tT_T}=DQ_{DPd}^{t} \tag{14}$$

The quantity of drugs delivered by a particular vehicle type is represented by β. There are two different modes of transportation, so these are added to obtain the total drug quantity delivered represented by DQ. These relationships are described in Eqs. (12) to (14). Parameters are listed in Table 5.

$$\beta_{WMd}^{tT_T}+\beta_{WMd}^{tT_A}=\chi.DQ_{MWd}^{t} \tag{15}$$
$$\beta_{DWd}^{tT_T}+\beta_{DWd}^{tT_A}=\chi.DQ_{WDd}^{t} \tag{16}$$
$$\beta_{PDd}^{tT_T}=\chi.DQ_{DPd}^{t} \tag{17}$$

Similarly, the quantity of the drug being recalled is shown in Eqs. (15) to (17). The quantity that can be recalled should be less than the quantity delivered to the buyer on order. This is managed by the variable χ, which has a value between 0 and 1 because the recalled drug should be lesser than or equal to the quantity delivered to the buyer. This indicates the percentage of drugs recalled from the delivered quantity initially. All the variables used in these equations are explained in Table 6.

Inventory cost at manufacturer due to recall =

$$\sum_{M}\sum\nolimits_{W}\sum_{t}(IC_{Md}^{t}\cdot(CS_{dM}^{t}+\chi.DQ_{MWd}^{t})) \tag{18}$$

The manufacturer has to bear extra inventory costs due to product recall presented in Eq. (18). This is calculated by adding the recalled quantity to the current stock of the manufacturer. This sum is multiplied by the inventory cost per unit drug to yield the extra inventory cost incurred to the manufacturer. The variables used in the equation are explained in Tables 2 and 4.

Table 7: Parameters involved in delivery cost due to recall

Notations	Descriptions
DC^{t}_{WMd}	Delivery cost of drug d from warehouse W to manufacturer M at time t.
DC^{t}_{DWd}	Delivery cost of drug d from distributor D to warehouse W at time t.
DC^{t}_{PDd}	Delivery cost of drug d from pharmacy P to distributor D at time t.
DQ^{t}_{WMd}	Delivered quantity of drug d by warehouse W to manufacturing unit M at time t.
DQ^{t}_{DWd}	Delivered quantity of drug d by distributor D to warehouse W at time t.
DQ^{t}_{PDd}	Delivered quantity of drug d by pharmacy P to distributor D at time t.
$TC^{tr_{WM}}_{WMdT_T}$	Transportation cost of drug d with transport type T_T from warehouse W to manufacturer M on route r_{MW} at time t.
$TC^{tr_{WM}}_{WMdT_A}$	Transportation cost of drug d with transport type T_A from warehouse W to manufacturer M on route r_{WM} at time t.
$TC^{tr_{DW}}_{DWdT_T}$	Transportation cost of drug d with transport type T_T from distributor D to warehouse W on route r_{DW} at time t.
$TC^{tr_{DW}}_{DWdT_A}$	Transportation cost of drug d with transport type T_A from distributor D to warehouse W on route r_{DW} at time t.
$TC^{tr_{PD}}_{PDdT_T}$	Transportation cost of drug d with transport type T_T from pharmacy P to distributor Don route r_{DP} at time t.

Delivery cost due to recall =

$$\sum_{M}\sum_{W}\sum_{t}(DC^{t}_{WMd}\cdot\chi.\,DQ^{t}_{WMd}) + \sum_{W}\sum_{D}\sum_{t}(DC^{t}_{DWd}\cdot\chi.\,DQ^{t}_{DWd}) + \sum_{D}\sum_{P}\sum_{t}(DC^{t}_{PDd}\cdot\chi.\,DQ^{t}_{PDd}) \tag{19}$$

The cost incurred to the manufacturer due to the delivery of a recalled drug is given in Eq. (19). It is calculated by adding the multiplied amount of recalled drugs and the drug delivery cost per unit quantity. The variables are listed in Table 7.

Transportation cost due to recall =

$$\begin{aligned}
&\sum_{M}\sum_{W}\delta_{MW}\,[(\sum_{M}\sum_{W}\sum_{t}\sum_{T_T}\beta^{tT_T}_{WMd}\cdot\sum_{r_{WM}}TC^{tr_{WM}}_{WMdT_T})\\
&\quad+(\sum_{M}\sum_{W}\sum_{t}\sum_{T_A}\beta^{tT_A}_{WMd}\cdot\sum_{r_{WM}}TC^{tr_{WM}}_{WMdT_A})]\\
&\quad+\sum_{W}\sum_{D}\delta_{WD}\,[(\sum_{W}\sum_{D}\sum_{t}\sum_{T_T}\beta^{tT_T}_{DWd}\cdot\sum_{r_{DW}}TC^{tr_{DW}}_{DWdT_T})\\
&\quad+(\sum_{W}\sum_{D}\sum_{t}\sum_{T_A}\beta^{tT_A}_{DWd}\cdot\sum_{r_{DW}}TC^{tr_{DW}}_{DWdT_A})]\\
&\quad+\sum_{D}\sum_{P}\delta_{DP}\,(\sum_{D}\sum_{P}\sum_{t}\sum_{T_T}\beta^{tT_T}_{PDd}\cdot\sum_{r_{PD}}TC^{tr_{PD}}_{PDdT_T})
\end{aligned} \tag{20}$$

In Eq. (20), the transportation cost owing to the drug recall is presented, which is calculated in the same way as the transportation cost is calculated for the forward chain. However, the recalled quantity is a fraction of the actual quantity delivered. The variables are taken from Tables 5, 6 and 7.

Total Recall cost =

$$
\begin{aligned}
&\sum_{\mathrm{M}} \sum\nolimits_{\mathrm{W}} \sum_{\mathrm{t}} (\mathrm{IC}^{\mathrm{t}}_{\mathrm{Md}} \cdot\ (\mathrm{CS}^{\mathrm{t}}_{\mathrm{dM}} +\ \chi.\, \mathrm{DQ}^{\mathrm{t}}_{\mathrm{MWd}}) \\
&\quad + \sum_{\mathrm{M}} \sum_{\mathrm{W}} \sum_{\mathrm{t}} (\mathrm{DC}^{\mathrm{t}}_{\mathrm{WMd}} \cdot \chi.\, \mathrm{DQ}^{\mathrm{t}}_{\mathrm{WMd}}) \\
&\quad + \sum_{\mathrm{W}} \sum_{\mathrm{D}} \sum_{\mathrm{t}} (\mathrm{DC}^{\mathrm{t}}_{\mathrm{DWd}} \cdot \chi.\, \mathrm{DQ}^{\mathrm{t}}_{\mathrm{DWd}}) + \sum_{\mathrm{D}} \sum_{\mathrm{P}} \sum_{\mathrm{t}} (\mathrm{DC}^{\mathrm{t}}_{\mathrm{PDd}} \cdot \chi.\ \mathrm{DQ}^{\mathrm{t}}_{\mathrm{PDd}}) \\
&\quad + \sum_{\mathrm{M}} \sum_{\mathrm{W}} \delta_{\mathrm{MW}} [(\sum_{\mathrm{M}} \sum_{\mathrm{W}} \sum_{\mathrm{t}} \sum_{\mathrm{T_T}} \beta^{\mathrm{tT_T}}_{\mathrm{WMd}} \cdot \sum_{\mathrm{r_{WM}}} \mathrm{TC}^{\mathrm{tr_{WM}}}_{\mathrm{WMdT_T}}) \\
&\quad + (\sum_{\mathrm{M}} \sum_{\mathrm{W}} \sum_{\mathrm{t}} \sum_{\mathrm{T_A}} \beta^{\mathrm{tT_A}}_{\mathrm{WMd}} \cdot \sum_{\mathrm{r_{WM}}} \mathrm{TC}^{\mathrm{tr_{WM}}}_{\mathrm{WMdT_A}})] \\
&\quad + \sum_{\mathrm{W}} \sum_{\mathrm{D}} \delta_{\mathrm{WD}} [(\sum_{\mathrm{W}} \sum_{\mathrm{D}} \sum_{\mathrm{t}} \sum_{\mathrm{T_T}} \beta^{\mathrm{tT_T}}_{\mathrm{DWd}} \cdot \sum_{\mathrm{r_{DW}}} \mathrm{TC}^{\mathrm{tr_{DW}}}_{\mathrm{DWdT_T}}) \\
&\quad + (\sum_{\mathrm{W}} \sum_{\mathrm{D}} \sum_{\mathrm{t}} \sum_{\mathrm{T_A}} \beta^{\mathrm{tT_A}}_{\mathrm{DWd}} \cdot \sum_{\mathrm{r_{DW}}} \mathrm{TC}^{\mathrm{tr_{DW}}}_{\mathrm{DWdT_A}})] \\
&\quad + \sum_{\mathrm{D}} \sum_{\mathrm{P}} \delta_{\mathrm{DP}} (\sum_{\mathrm{D}} \sum_{\mathrm{P}} \sum_{\mathrm{t}} \sum_{\mathrm{T_T}} \beta^{\mathrm{tT_T}}_{\mathrm{PDd}} \cdot \sum_{\mathrm{r_{PD}}} \mathrm{TC}^{\mathrm{tr_{PD}}}_{\mathrm{PDdT_T}})
\end{aligned}
\tag{21}
$$

The total cost depends upon the costs incurred in both the forward and backward chains. The backward chain cost, i.e., recalled cost includes the materialistic loss the company has to incur in terms of providing the reimbursements or exchanged products. The total cost involved in recalling the product is calculated by Eq. (21). This is calculated by adding costs determined by Eqs. (18) to (20).

Table 8: Parameters involved in recall time

Notations	**Descriptions**
$\tau^{T_T}_{WMr_{WM}}$	Travel time from warehouse W to manufacturing unit M on route r_{WM} with transport T_T.
$\tau^{T_A}_{WMr_{WM}}$	Travel time from warehouse W to manufacturing unit M on route r_{WM} with transport T_A.
$\tau^{T_T}_{DWr_{DW}}$	Travel time from distributor D to warehouse W on route r_{DW} with transport T_T.
$\tau^{T_A}_{DWr_{DW}}$	Travel time from distributor D to warehouse W on route r_{DW} with transport T_A.
$\tau^{T_T}_{PDr_{PD}}$	Travel time from pharmacy P to distributor D on route r_{PD} with transport T_T.

Recall time =

$$
\begin{aligned}
&\sum_{M} \sum_{W} \sum_{T_T} (\sum_{t} \beta^{tT_T}_{WMd} \cdot \sum_{r_{WM}} \tau^{T_T}_{WMr_{WM}}) \\
&\quad + \sum_{M} \sum_{W} \sum_{T_A} (\sum_{t} \beta^{tT_A}_{WMd} \cdot \sum_{r_{WM}} \tau^{T_A}_{WMr_{WM}}) + \sum_{W} \sum_{D} \sum_{T_T} (\sum_{t} \beta^{tT_T}_{DWd} \cdot \sum_{r_{DW}} \tau^{T_T}_{DWr_{DW}}) \\
&\quad + \sum_{W} \sum_{D} \sum_{T_A} (\sum_{t} \beta^{tT_A}_{DWd} \cdot \sum_{r_{DW}} \tau^{T_A}_{DWr_{DW}}) + \sum_{D} \sum_{P} \sum_{T_T} (\sum_{t} \beta^{tT_T}_{PDd} \cdot \sum_{r_{PD}} \tau^{T_T}_{PDr_{PD}})
\end{aligned}
\tag{22}
$$

Eq. (22) indicates the time required to complete the recall procedure, collecting the recalled drug from the pharmacy level to the manufacturer's end. The variables are taken from Tables 6 and 8.

The total cost and time involved in the pharmaceutical supply chain, including the cost and time in the forward chain and the extra cost and time due to the drug recall, are given in Eq. (23) and Eq. (24).

$$Total\ cost\ =\ Total\ end-to-end\ cost\ in\ the\ forward\ chain\ +\ \mu\ *\ (Total\ Recall\ Cost) \tag{23}$$

where the total end-to-end cost is given in Eq. (10), the total recall cost is determined in Eq. (21), and μ is a Boolean variable (0 or 1) to indicate whether a drug recall is involved in the network or not.

Total time = Total delivery time + μ * (Total Recall time) =

$$\begin{aligned}&\sum_M \sum_W \sum_{T_T}(\sum_t \beta_{MWd}^{tT_T} \cdot \sum_{r_{MW}} \tau_{MWr_{MW}}^{T_T}) + \sum_M \sum_W \sum_{T_A}(\sum_t \beta_{MWd}^{tT_A} \cdot \sum_{r_{MW}} \tau_{MWr_{MW}}^{T_A}) + \\ &\sum_W \sum_D \sum_{T_T}(\sum_t \beta_{WDd}^{tT_T} \cdot \sum_{r_{WD}} \tau_{WDr_{WD}}^{T_T}) + \sum_W \sum_D \sum_{T_A}(\sum_t \beta_{WDd}^{tT_A} \cdot \sum_{r_{WD}} \tau_{WDr_{WD}}^{T_A}) + \\ &\sum_D \sum_P \sum_{T_T}(\sum_t \beta_{DPd}^{tT_T} \cdot \sum_{r_{DP}} \tau_{DPr_{DP}}^{T_T}) + \mu\{\sum_M \sum_W \sum_{T_T}(\sum_t \beta_{WMd}^{tT_T} \cdot \sum_{r_{WM}} \tau_{WMr_{WM}}^{T_T}) + \\ &\sum_M \sum_W \sum_{T_A}(\sum_t \beta_{WMd}^{tT_A} \cdot \sum_{r_{WM}} \tau_{WMr_{WM}}^{T_A}) + \sum_W \sum_D \sum_{T_T}(\sum_t \beta_{DWd}^{tT_T} \cdot \sum_{r_{DW}} \tau_{DWr_{DW}}^{T_T}) + \\ &\sum_W \sum_D \sum_{T_A}(\sum_t \beta_{DWd}^{tT_A} \cdot \sum_{r_{DW}} \tau_{DWr_{DW}}^{T_A}) + \sum_D \sum_P \sum_{T_T}(\sum_t \beta_{PDd}^{tT_T} \cdot \sum_{r_{PD}} \tau_{PDr_{PD}}^{T_T})\}\end{aligned} \tag{24}$$

Similarly, the total time involved in the network is calculated by summing the total delivery time and the total recall time. This is done by summing up the Eqs. (11) and Eq. (22). Eq. (24) gives the total time involved in the forward chain and the backward chain. The occurrence of the backward chain depends upon the occurrence of the recall procedure denoted by μ.

4. Performance Analysis

This section discusses the performance analysis of the proposed scheme.

4.1 Experimental Setup

The Hyperledger Composer [55] was used to develop the blockchain-based network on a Dell Optiplex 7050 MT desktop with Linux Ubuntu 20.04 (Focal Fossa) as an operating system, 9th Generation Intel Core i3-9100 Processor (3.60 GHz), 32GB RAM, and 2TB HDD. The Hyperledger Composer contains a unique set of necessary files for the blockchain network to run an application [56]. For testing purposes, SOLO was used, which requires a single ordering node. During production, SOLO can be easily replaced with Kafka [57] to enable multiple ordering nodes in a chain. Here, the admin, i.e., the local system, also acts as an ordering node.

4.2 Results and Discussion

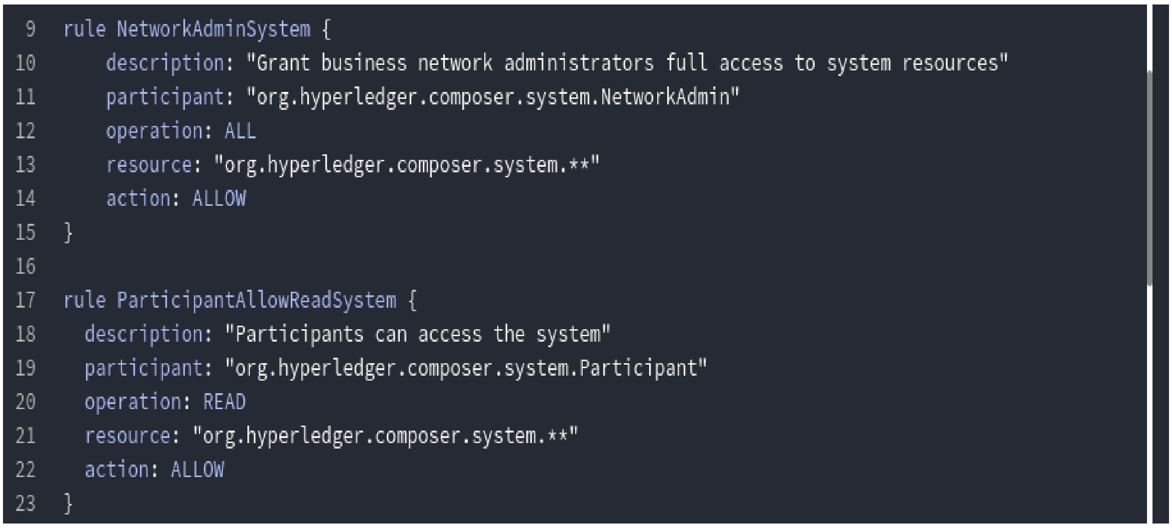
The Hyperledger contains an object-oriented modeling language file (CTO file) that is responsible for declaring the assets, transactions, and rules to be followed in the blockchain network. In the experiment, 'Drug' is the asset, which is under consideration and uniquely identified by a string variable, i.e., 'drugId'. A drug has multiple fields, such as name, batch number, description, quantity, and the current owner in the supply chain. There are multiple participants in this network, which are defined in the CTO file in Table 9.

Table 9: Participants in the network

Participant	Property	Object type of property
Drug	drugId	String
	name	String
	batchNo	String
	description	String
	itemCondition	Function
	quantity	Double
	owner	Instance of the abstract function ChainMember
ChainMember (RawProductSupplier, Manufacturer, Warehouse, Distributor and Pharmacy extends this class)	Id	String
	name	String
	email	String
	address	String
	accountBalance	Double
Warehouse	centigrade	Double
	capacity	Double

In the network, the ChainMember is identified by a string variable 'Id'. There cannot be any other participant with the name 'ChainMember', however, this participant can be used as a reference class for other participants in the network. All other participants can inherit all the properties of ChainMember along with the properties defined specifically for a particular participant. As shown in Table 9, the 'RawProductSupplier', 'Manufacturer', 'Warehouse', 'Distributor', and 'Pharmacy' inherit properties of 'ChainMember' and 'Warehouse' declares other parameters like 'centigrade' and 'capacity', denoting the temperature and capacity of the warehouse, respectively.

The Hyperledger Composer also uses the ACL file, which is responsible for setting up the read and write privileges for different participants in the network. As shown in Figure 5, the rules within the ACL file are used to define all reading, or viewing, and writing privileges in the network, where the network admin has the privilege to access all the system resources, but participants in the network can only read the system resources. The entire processing of the blockchain network is coded in a JavaScript file named 'logic.js'. All the works are executed based on the functionalities defined in this file. In the 'payOut' function, the account balance and the quantity are checked. If these values are validated, the amount and quantity from the sender are reduced and then added to the receiver's inventory. Finally, the ownership of the drug is transferred from the sender to the receiver.



```
rule NetworkAdminSystem {
    description: "Grant business network administrators full access to system resources"
    participant: "org.hyperledger.composer.system.NetworkAdmin"
    operation: ALL
    resource: "org.hyperledger.composer.system.**"
    action: ALLOW
}

rule ParticipantAllowReadSystem {
  description: "Participants can access the system"
  participant: "org.hyperledger.composer.system.Participant"
  operation: READ
  resource: "org.hyperledger.composer.system.**"
  action: ALLOW
}
```

Figure 5: Privileges in the ACL file

Table 10 shows the entities of the test environment, which includes participants and transactions in the network. The first participant is the manufacturer 'Abbott,' which contains all the required fields mentioned in the CTO file, like 'Id,' 'email,' 'address,' and 'accountBalance'. Similarly, one record for each participant is created to show the entire working process of the supply chain. A drug with the id 'Drug1' and name "Anafortan" is created and includes the batch number, drug description, item condition, quantity, and the current owner to show its movement in the forward and backward chains.

Table 10: Entity in the test environment

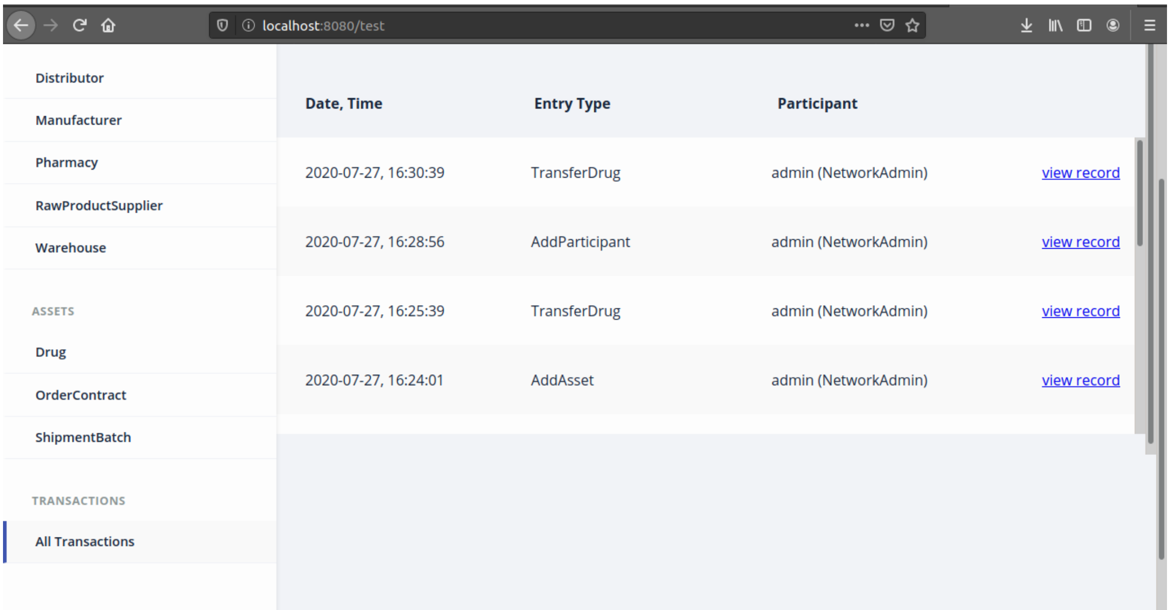
Entity	Property	Value
Manufacturer	class	org.example.mynetwork.Manufacturer
	Id	M1
	name	Abbott
	email	manu@abbott.com
	address	class: org.example.mynetwork.Address
		Country: India
	accountBalance	1,000,000
Drug	class	org.example.mynetwork.Drug
	drugId	Drug1
	name	Anafortan
	batchNo	Batch1
	description	Camylofin 25 mg + Paracetamol 300 mg
	itemCondition	class: org.example.mynetwork.ItemCondition
		conditionDescription:” ”
		status: GOOD
	quantity	10,000
	owner	resource: org.example.mynetwork.Warehouse#W1
Transaction	class	org.example.mynetwork.TransferDrug
	drugId	resource:org.example.mynetwork.Drug#Drug1
	newowner	resource:org.example.mynetwork.Distribution#D1
	shipment	resource:org.example.mynetwork.shipmentBatch#Sh2

Table 10 also indicates that the current owner of Drug1 is Warehouse W1, which can be seen in the 'owner' label in the 'Drug' asset. Here, a transaction to transfer the drug within the network from one participant to another is shown. Each of the transactions in the drop-down list has a separate function in the 'logic.js' file, where a transaction is executed to transfer a drug from Warehouse W1 to Distributor D1. When the transaction is completed, the ownership of the drug is automatically changed in the 'Drug' asset from Warehouse W1 to Distributor D1, as shown in Table 11.

Figure 6 displays the transaction history, which never gets deleted from the blockchain network, and each action in the supply chain is logged. The creation of every participant, asset, and the submitted transaction is always available. Further details of each transaction can be seen by using the 'view record' option shown to the right of each transaction. It can be seen that all the transactions are executed by the admin. Considering that the main purpose of this proposed scheme is to provide a solution for the drug recall supply chain, this blockchain consists of a super-node called 'admin' that is allowed all privileges to ensure the recall process is optimized. The proposed solution can be implemented with different nodes in action using 'Apache Kafka,' as stated above.

Table 11: Updated attributes after drug transfer

Entity	Property	Value
Drug	class	org.example.mynetwork.Drug
	drugId	Drug1
	name	Anafortan
	batchNo	Batch1
	description	Camylofin 25 mg + Paracetamol 300 mg
	itemCondition	class: org.example.mynetwork.ItemCondition
		conditionDescription: “ ”
		status: GOOD
	quantity	10,000
	owner	resource: org.example.mynetworkDistributor#D1
OrderContract	class	org.example.mynetwork.OrderContract
	orderId	Ord1
	buyer	resource:org.example.mynetwork.Pharmacy#P1
	seller	resource:org.example.mynetwork.Distributor#D1
	expectedArrivalLocation	resource:org.example.mynetwork.Location
		globalLN: 110007
		Address class: org.example.mynetwork.Address country: India
	payOnArrival	True
	arrivalDateTime	2020-07-T05:14:25.902Z
	quantity	100
	paymentPrice	2,000



Date, Time	Entry Type	Participant	
2020-07-27, 16:30:39	TransferDrug	admin (NetworkAdmin)	view record
2020-07-27, 16:28:56	AddParticipant	admin (NetworkAdmin)	view record
2020-07-27, 16:25:39	TransferDrug	admin (NetworkAdmin)	view record
2020-07-27, 16:24:01	AddAsset	admin (NetworkAdmin)	view record

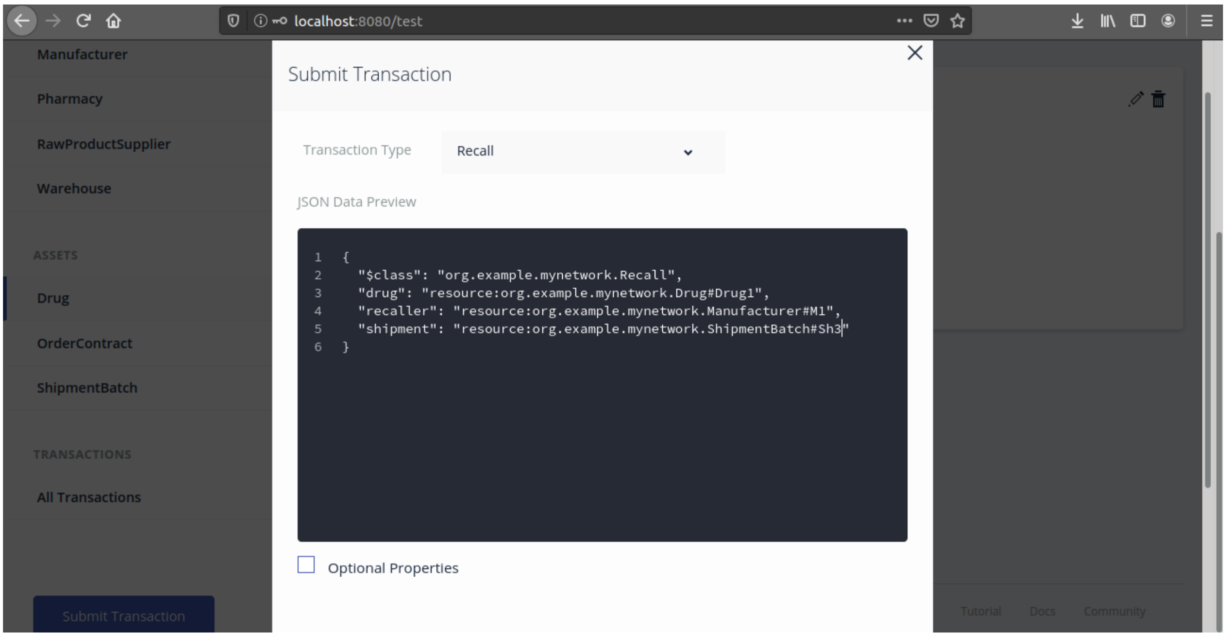
Figure 6: Transaction history of all the events in the supply chain

Since the order contracts enable the viewer to see all details about a drug, including its owner, transparency is maintained in the system. Suppose that Pharmacy P1 places a contract with Distributor D1, then the asset 'OrderContract' is invoked. The order contracts also show information about the buyer, seller, arrival location, a Boolean entry payOnArrival, arrival date, quantity ordered, and payment price made for the total order, further contributing to the system's transparency. After an order is placed, it is the responsibility of the seller to create an order and to add the contract, i.e.

transaction, into the blockchain network. The order and shipment contract is created by the seller, as shown in Table 12.

Table 12: Updated attributes after delivery to pharmacy

Entity	Property	Value
Drug	class	org.example.mynetwork.Drug
	drugId	Drug1
	name	Anafortan
	batchNo	Batch1
	description	Camylofin 25 mg + Paracetamol 300 mg
	itemCondition	class: org.example.mynetwork.ItemCondition
		conditionDescription: “ “
		status: GOOD
	quantity	10,000
	owner	resource: org.example.mynetwork.Pharmacy#P1



Submit Transaction

Transaction Type: Recall

JSON Data Preview

```
{
  "$class": "org.example.mynetwork.Recall",
  "drug": "resource:org.example.mynetwork.Drug#Drug1",
  "recaller": "resource:org.example.mynetwork.Manufacturer#M1",
  "shipment": "resource:org.example.mynetwork.ShipmentBatch#Sh3"
}
```

☐ Optional Properties

Figure 7: Transaction recall under execution

All transactions that have been shown up to this point are executed in the forward chain, thus drug recall has not yet been considered. The backward chain concerns the recall process, which is executed using the 'RecallDrug' function that provides similar functionalities to the 'TransferDrug' function, except that it includes the reverse flow of a drug from a pharmacy to the manufacturer. As shown in Table 13, 'Drug1' is currently possessed by Pharmacy P1, for which a transaction to recall the drug requires the shipment Id as the input. A corresponding transaction log is demonstrated in Figure 7.

When the transaction is executed, it is logged in the transaction history, shown in Figure 6 and the ownership of drug 'Drug1' is changed from Pharmacy P1 to Manufacturer M1 in Table 13. Thus, the drug recall process on the pharmacy level is completed. This procedure can be executed at each level, i.e. Pharmacy, Distributor, etc., to recall the drug. If a company wants to know that whether the drug is faulty before it reaches the pharmacy, the drug recall can be initiated starting with the distributor before it goes deeper into the supply chain. This process is iteratively repeated until the manufacturer collects all faulty drug units from every entity involved in the supply chain. Finally, the manufacturer conducts investigative analysis for recall and audits to ensure that the backward chain reflects the actual costs and time that were supposed to be. In standard cases, the auditing for the forward chain goes as usual (yearly or half-yearly) using the mathematical model developed for the forward supply chain. For the sake of simplicity, only a single unit of each supply chain participant has been considered in this study.

Table 13: Updated attributes after drug recall

Entity	**Property**	**Value**
Drug	Class	org.example.mynetwork.Drug
	drugId	Drug1
	Name	Anafortan
	batchNo	Batch1
	Description	Camylofin 25 mg + Paracetamol 300 mg
	itemCondition	class: org.example.mynetwork.ItemCondition
		conditionDescription: “ “
		status: GOOD
	Quantity	10,000
	Owner	resource: org.example.mynetwork.Manufacturer#M1

4.2.1 Results

It is vital to gauge the performance of a solution. This subsection explains the results obtained after a thorough analysis of different factors.

The performance of the proposed technique was further compared with three state-of-the-art techniques in terms of query transaction, invoking transaction, total latency, and throughput. The query transaction latency and transaction invoking latency represent delays in the process and invoking the transaction. The query transaction is computed as the delay to execute a transaction on the server, while the time taken to initiate the transaction is considered as the transaction invoking latency. The total latency represents the total delay in performing a transaction and it is computed by adding the query transaction and transaction invoking latency; all latencies are measured in seconds. The throughput exhibits the number of transactions executed per second. The analysis was performed by considering different scenarios and varying the number of users from 100 to 5000 to show the scalability of the proposed strategy.

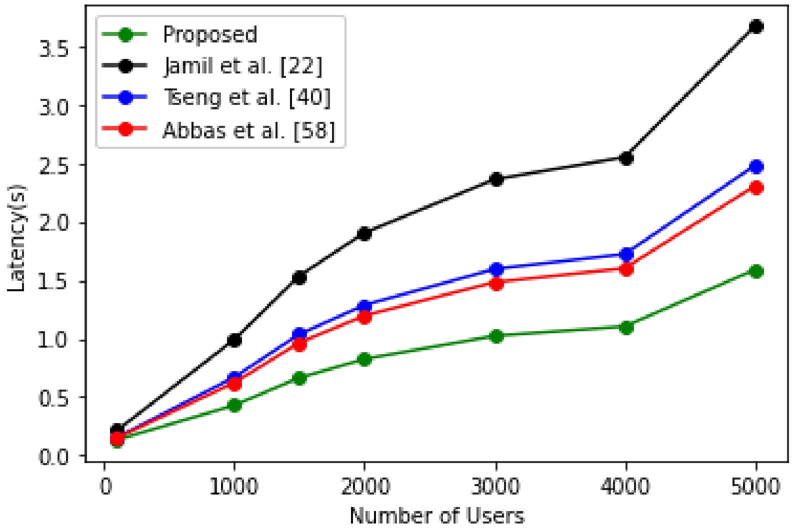


Figure 8: Comparison of latency in query transaction

Figure 8 presents a comparative analysis of the proposed strategy with previously reported methods in terms of the query transaction latency for an increasing number of users. It can be seen that the average latency increases with the number of users. For instance, the average delay was estimated to be 1.5 s, when the number of users was around 5000 and was, only 0.1 s for 100 users. Our strategy reduced the latency in query transactions by 31.7% compared to the other state-of-the-art techniques.

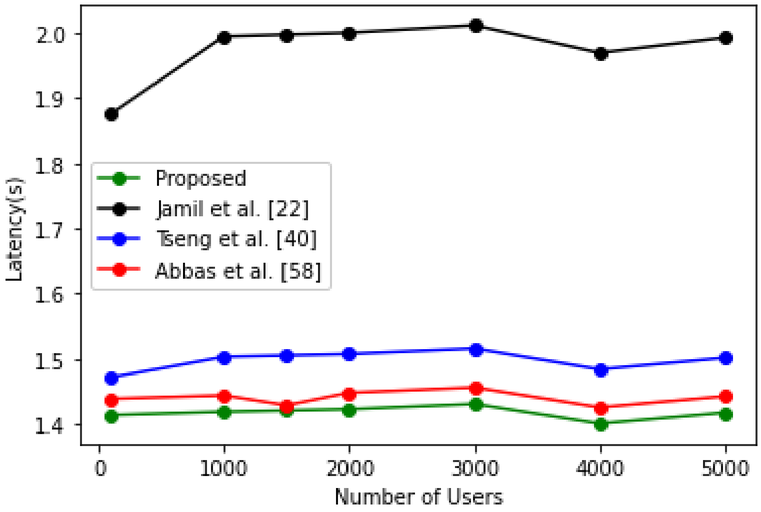


Figure 9: Comparison of latency in invoking transaction

Figure 9 shows the comparison of latency for invoking a transaction with different numbers of users. It can be observed that transaction invocation time remained almost the same as the number of users increased. Moreover, our proposed strategy reduced the transaction invocation time compared to the techniques proposed in other studies.

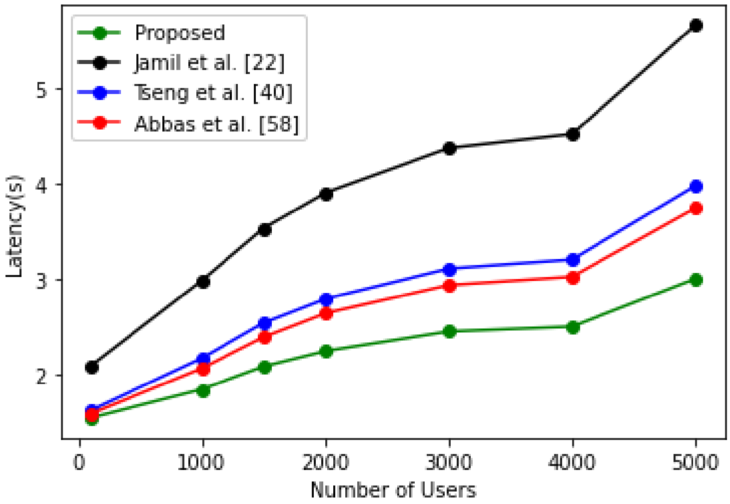


Figure 10: Comparison of the total latency for different number of users

Figure 10 presents the comparison of total latency, including the invoking transaction latency and processing transaction latency. It can be observed that the variation in total latency is similar to the variation in query transaction latency with different numbers of users. This is because invoking transaction latency is independent of the number of users, which explains the results in Figure 9.

Figure 11 illustrates the results for the throughput, measured in Transactions Per Seconds (TPS), for different numbers of users. It is apparent that the throughput increases as the number of users in the network increases, which attributes to the enhanced data flow when there are more users. Specifically, more than 500 transactions were executed per second when 5000 users were simultaneously active, thus demonstrating the effectiveness of the proposed strategy. Moreover, our technique yielded a 12.4% improvement compared to the scheme of Abbas et al. [58].

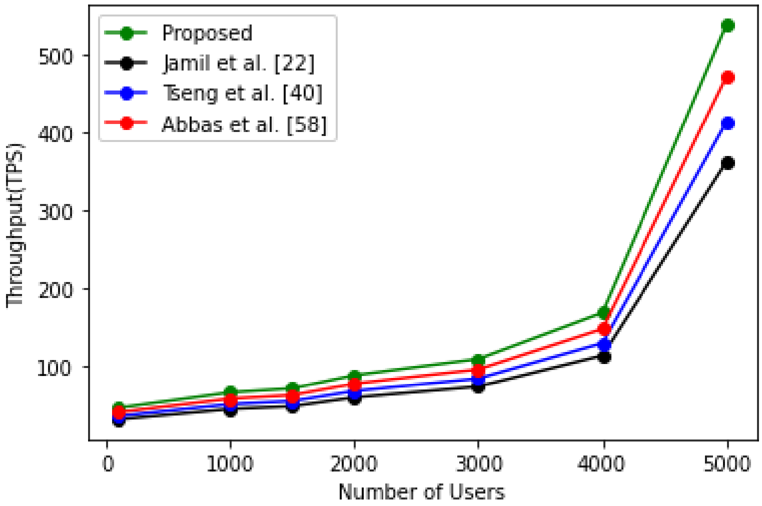


Figure 11: Throughput analysis for different number of users

Table 14: Comparison of the proposed scheme with state-of-the-art techniques

Attributes	**Jamil et al.** [22]	**Tseng et al.** [40]	**Abbas et al.** [58]	**Proposed**
Consensus Mechanism	Selected Participants	Complete Participants	Random Participants	Random Participants
Working	Drug supply chain management	Drug supply chain management	Drug supply chain management	Drug supply chain management and recall
Efficacy	High	Low	High	Very High
Network Type	Permissioned	Permissionless	Permissioned	Permissioned
Recall	✗	✗	✗	✓

Table 14 compares the proposed scheme with state-of-the-art techniques regarding efficacy, recall, network type, working and consensus mechanism. The scheme proposed by Jamil et al. [22] performs the consensus mechanism on the selected participants of the network and exhibits high efficacy. Abbas et al. [58] have used the consensus mechanism on the randomly selected participants. In contrast, the scheme suggested by Tsend et al. [40] applies the consensus mechanism to all the participants of the network. The efficacy of the proposed scheme is very high, i.e. better than all the other state-of-the-art techniques due to the drug recall and blockchain implementation. The proposed scheme implements the recall procedure, which is not implemented in any of the state-of-the-art techniques. The results suggest that the proposed scheme effectively implements the recall procedure in the blockchain-based supply chain management and achieves high efficiency by using random participants for the consensus mechanism.

5. Conclusions and Future Works

The menacing presence of fake drugs in the pharmaceutical market can lead to dangerous side effects that can cause health issues and even death. This work proposes a novel blockchain-based supply chain process that effectively implements drug recall for the pharmaceutical sector. Importantly, this strategy supports secure and transparent transactions that benefit every stakeholder in the supply chain process by allowing the manufacturer to quickly identify a fake drug, which usually goes unnoticed in the traditional supply chain process. The proposed strategy achieves effective drug recall, the incorporated forward and backward supply chain management systems reduce costs and time with increasing transportation reliability. The models also play a vital role in conducting financial audits. The manufacturer could easily identify the defaulter (if any) as all the transactions are publicly stored over the blockchain network. The Hyperledger Composer was utilized to implement the proposed scheme, revealing that it can be easily applied in the pharmaceutical sector. The maximum and average latency and throughput were further analyzed by varying the number of users from 100 to 5000. Compared to existing state-of-the-art techniques, the proposed strategy improved average throughput by 12.4% and reduced query transaction and invoked transaction latencies by 31.7% and 1.7%, respectively, further confirming the proposed technique's effectiveness. The scope of this study is limited to domestic business, i.e. all the participating stakeholders must be within a country. However, it could be extended to cross-trade business with business entities spanning across the world. To avoid extra storage costs and spaces, manufacturers tend to outsource the warehousing to a third party. Thus, the warehouse becomes a separate entity and can create security issues. A novel consensus algorithm can be developed in the future to process all transactions of the pharmaceutical sector automatically.

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