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PharmaChain 3.0: Efficient Tracking and Tracing of Drugs in Pharmaceutical Supply Chain using Blockchain Integrated Product Serialization Mechanism

Anand Kumar Bapatla · Saraju P. Mohanty⋆ · Elias Kougianos

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Abstract Globalization has revolutionized how different entities are distributed across locations interconnect and collaborate to enhance the availability of different services even at remote areas. Supply chains have played an important role in expanding business operations globally and at the same time increasing operational efficiency and reducing costs. Pharmaceutical Supply Chain (PSC) is one of the important aspects of healthcare which is vital for resource acquisition, manufacturing, and distribution of prescription drugs from the manufacturer site to patients. "Five rights of medication" is the main motto of the PSC which ensures the delivery of the right medicine to the right patient, at the right time, in the right doses, and through the appropriate route. Following this principle achieves patient safety in the healthcare system. However, as the number of entities participating in the PSC is large, which are geographically distributed and interact in complex ways makes the PSC more abstract and causes adversaries to introduce counterfeit medicines into the system. Developing a transparent PSC with no information fragmentation is very much needed for efficient track and trace along with easy identification and avoidance of counterfeit drugs. The current paper proposes one such architecture that is integrated with Blockchain, Distributed File Storage System, and Barcode technologies to provide a secure Barcode mechanism for addressing such tracking and tracing issues in the pharmaceutical supply chain. The novel product serialization mechanism proposed in PharmaChain 3.0 also ensures accurate identification, capture, and sharing of information about the drugs manufactured between these participating entities without the use of centralized entities and removing blind parties. The current system is designed to efficiently capture both Pedigree and T3 information of drugs in order to comply with regulations like Drug Supply Chain Security Act (DSCSA) and Prescription Drug Marketing Act (PDMA). Further, we have developed a proof-of-concept for the proposed system, and evaluation is performed focusing on the different aspects including system functionality, security, cost of execution, and adaptability.

Keywords Pharmaceutical Supply Chain, Blockchain, Distributed Ledger Technologies, Ethereum, Smart Contracts, Product Serialization, Barcode Mechanism, Drug Labeling

Anand Kumar Bapatla
Dept. of Computer Sci. and Eng., University of North Texas
E-mail: anandkumarbapatla@my.unt.edu

Saraju P. Mohanty (Corresponding Author)
Dept. of Computer Sci. and Eng., University of North Texas
E-mail: saraju.mohanty@unt.edu

Elias Kougianos
Dept. of Electrical Eng., University of North Texas
E-mail: elias.kougianos@unt.edu

1 Introduction

A pharmaceutical supply chain (PSC) is a special supply chain that typically involves the process of sourcing raw materials, manufacturing, distributing, and delivery of medication to patients. It is one of the important components of the healthcare system to ensure the drugs are reached at the right place at the right time in the right quantities at an optimal cost for patients [19]. The PSC encompasses a wide heterogeneous product with different drug compositions, manufacturing processes, and distribution channels to the patients. PSC is very complex with a variety of actors participating in the process which interact in very complex ways.

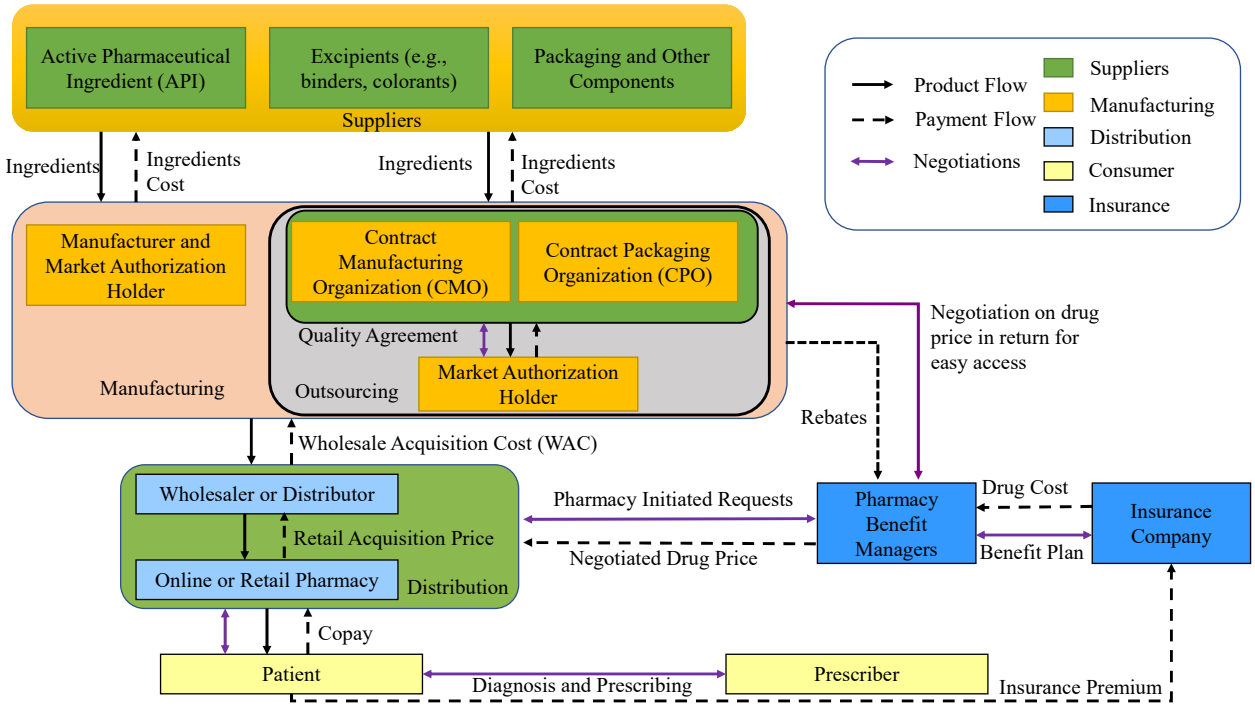

Fig. 1: Typical Pharmaceutical Supply Chain With Product and Payment Flows

All these interactions within the pharmaceutical supply chain can be classified into three main flows which include Material, Information, and funds. Information flow is one of the important aspects of PSC to reduce risks [37]. A typical pharmaceutical supply chain and flow of materials and funds is shown in Figure 1 which doesn't cover reverse logistics for simplicity. A market authorization holder is an entity that has approval from U.S. Food and Administration (FDA) to manufacture and market the drugs. In a simple scenario, the market authorization holder is considered a manufacturer who carries out sourcing of all the chemical and packaging ingredients, combining ingredients based on the formulary to capsules or pills. Packaging and labeling of the finished drugs are also taken care of by the manufacturer. In the case of outsourcing, two new entities can be seen among which Contract Manufacturing Organization (CMO) is responsible for gathering chemical ingredients and performing the manufacturing, and Contract Packaging Organization (CPO) is responsible for packaging and labeling. APIs are chemicals that are required for treating a health condition. These API suppliers also must undergo scrutiny from FDA using the drug master file (DMF) before being listed as authorized suppliers to the manufacturer [15]. Excipients are the chemical compositions used for bindings, color, and flavoring for drugs. Distribution logistics might vary widely based on the type of drugs being distributed. In the most common scenario, manufacturers sell and transport the drugs to distributors or wholesalers at wholesale acquisition cost. Transportation is generally managed by third-party logistics (3PL) and reaches the point of dispensing either it is online or in retail pharmacies. Distributors maintain 30 days of supply, in order to maintain smooth supply in case of demand. In some special scenarios, specialty drugs are directly sent from manufacturers to hospitals or specialty pharmacies.

Most commonly drugs are dispensed through retail pharmacies which have brick and motor establishments. Along with these, some portions of drugs are dispensed from mail-order pharmacies. Pharmacies, unlike distributors, carry a short-term inventory to meet the demand and receive shipments frequently from distributors. Pharmacy Benefit Managers (PBMs) are responsible for building and managing these pharmacy networks. Along with that, another important role of PBMs is in negotiating drug prices with market authorization holders in return for access to the markets. This rebate negotiated will be made available to the payers to reduce the drug cost significantly. They are also responsible for creating benefit plans and working with the insurance providers.

Types of drugs involved in PSC include prescription drugs, Over the counter (OTC), and Complementary medicines. Prescription drugs are for the treat-

ment of a wide variety of chronic and life-threatening health conditions and would require a prescription by an authorized practitioner. Typically these prescription drugs are regulated by federal agencies like U.S. Food and Administration (FDA) through New Drug Application (NDA) which includes all animal and human trial information before being approved to manufacture and supply to the patients [16]. OTC drugs on the other hand treat multiple symptoms like allergies, colds etc., and don't require a prescription from the practitioner, and can be bought directly off-the-shelf in stores and pharmacies. These OTC drugs are regulated by drug monographs which include the acceptable ingredients and formulations listed in OTC drug monographs. Drugs that are produced following the monographs can be marketed without any further approvals.

1.1 Challenges and Issues in PSC

As we can see, the PSCs are complex due to the large number of distributed entities participating and interacting in complex ways. This obscurity causes one of the important threats in healthcare which is counterfeits [9]. According to World Health Organization (WHO), counterfeits are defined as medicines produced in substandard conditions using fewer quantities of required ingredients (API) or no API or a more serious scenario of repackaging the expired medicines to introduce back into the supply chain [24]. These counterfeit drugs have a very significant impact on the health of patients and can even lead to several causalities. Due to the complexity of the PSC, identifying and punishing entities introducing counterfeit drugs into the supply chain is very difficult. According to WHO, it is estimated around one in every 10 medical products sold in low and middle-income countries is reported as counterfeits [24]. Consumption of counterfeit drugs can cause many issues which include: adverse health conditions, drugs cannot cure diseases, financial loss, degrading belief in healthcare system and sometimes severe microbial infections to patients. Some of the significant challenges associated with Pharmaceutical Supply Chain are:

- Counterfeit Drugs: One of the most significant challenges in PSC is Counterfeit drugs. These are drugs that are deliberately mislabeled or misrepresented and may contain incorrect ingredients which can lead to treatment failure and harm patients.
- Lack of Traceability: Current PSC lack end-to-end transparency that makes difficulty in verifying the authenticity of the drugs throughout the supply chain. This lack of visibility can lead to counterfeits being introduced into the supply chain.

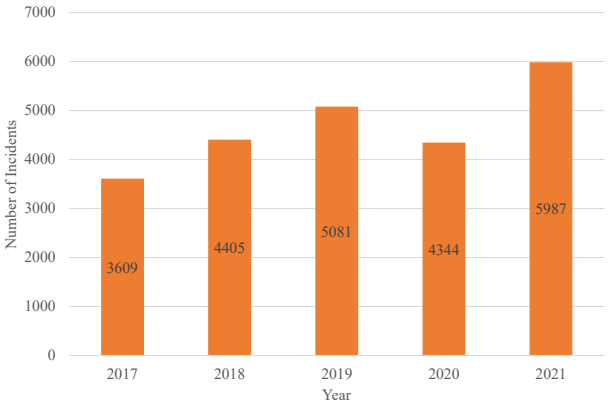

Fig. 2: Pharmaceutical Incident Trends from PSI Data

- Serialization: Serialization involves assigning a unique identifier to the items that can help in tracking and tracing. Current serialization systems are expensive to implement and require co-ordination between multiple stakeholders.
- Consumer Education: Patients or end consumer lacks tools to verify the authenticity of the product. Managing and distributing the drug usage instructions is difficult and some times prone to errors misplacing the information leaflets.
- Lack of Standardization: Multiple centralized PSC management systems follow different data formats and communication protocols. This lack of standardization makes it difficult for interoperability, introduce delays, and hinders real-time tracking of products.
- Globalization: Globalization has increased the risk of counterfeits as the drugs are often passed through numerous countries and intermediaries.
- Data Security: Centralized systems are prone to different security threats which could lead to data security. Unwanted manipulation of data not only facilitate introducing counterfeit drugs but also causes significant financial loses.
- Regulatory Compliance: Compliance with regulations is very challenging especially for multinational supply chains that must adhere different regulations in different countries.

1.2 Motivation

According to [28] it is estimated around 122,350 child deaths are associated in 39 sub-Saharan countries due to counterfeit anti-malarial drugs. Another survey [27] which has analyzed 48 such incidents both in developing and developed countries has involved approxi-

mately 7200 casualties including 3604 deaths. This survey shows counterfeiting is not only a problem in low-income and mid-income countries but also prevalent in developed countries. The Pharmaceutical Security Institute (PSI) which is a non-profit organization has collected the incidents related to counterfeiting and the number of incidents per year is plotted [18]. Figure 2 clearly shows a 38% increment in the number of incidents in CY2021 among which 2442 incidents are reported in North America followed by Asia Pacific with 1747 incidents. These statistics clearly show the severity of counterfeits and their impact on the whole world.

Product serialization is process of assigning unique identifier to each individual unit and lots to enhance traceability and avoid counterfeiting. It is one of the central requirements of the Drug Supply Chain Security Act (DSCSA) which mandates manufacturer to apply a unique product identifier that includes alphanumeric code. The cost of implementing serialization in PSC vary depending on many factors including Scale of Operations, Type of Product, Regulatory Requirements, Technology, Software, Hardware, Data Management, Training, Workforce, and integration with existing systems. As discussed in [35], it is estimated the total cost of ownership for serialization software is 10 times more than the initial acquisition cost. Pharmaceutical companies vary from small scale to large scale in range of $1,00,000 to several million dollars including initial implementation and annual costs. According to report from European Pharmaceutical Industries and Association (EFPIA), initial serialization implementation costs for large scale pharmaceutical company is €125 million and a recurring cost of 1.6 cents per pack of medicine. Not only serialization software, unique identifiers need to be purchased. According to GS1 US [36] 100,000 unique identifiers need initial fee of $10,500 and annual renewal fee of $2100. Considering the fact that millions of units are produced daily and need for maintaining the tracking information for 12 years make it an expensive recurring cost in pharmaceutical supply chains.

1.3 Contributions

Keeping the problem of counterfeits in mind, regulatory agencies like FDA have implemented some rules like Drug Quality and Security Act (DQSA). Blockchain is one of the recent technologies which can help to build a transparent supply chain and avoid counterfeits in PSC. Current paper proposes one such blockchain application combined with novel product serialization technique to provide efficient tracking and tracing in PSC. Some of the major contributions of PharmaChain 3.0 are listed below:

- Blockchain-based Digital Twinning: Utilizing smart contract addresses as serialization number for units and lots creates digital twins. These digital twins provide better management and traceability.
- Digital-twin also helps in avoiding the serialization costs which is significant recurring cost in Pharmaceutical manufacturing.
- Unit-level Traceability: Proposed Smart Contracts based on factory contract design pattern allows both unit and lot level traceability unlike other solutions which provide only lot level traceability.
- All the transaction T3 information, drug pedigrees and usage information are managed in current implementation using both on-chain and off-chain storage that is novel compared to the other implementations.

1.4 Organization of Paper

The rest of the paper is organized as follows: Section 2 presents materials that will help to understand the reader the technicalities of this paper. Section 3 discusses different proposed solutions both based on DLT and non-DLT for pharmaceutical supply chain integrity. Section 4 clearly describes the problems addressed by the proposed PharmaChain 3.0. Section 5 presents the architectural overview and methods proposed in PharmaChain 3.0. Section 6 discuses the implementation details extensively along with implemented smart contracts. Section 7 presents the functional testing, cost, and reliability of the proposed PharmaChain 3.0 solution. Section 8 discussed the limitations and challenges of PharmaChain 3.0 and Section 9 provides the conclusion of the paper along with possible future research directions.

2 Background Materials

2.1 Drug Quality and Security Act (DQSA)

Drug Quality and Security Act (DQSA) was enacted in 2013 as a response to a nationwide fungal outbreak due to the distribution of contaminated steroidal injections which lead to 64 fatalities and 793 patients with infection [14]. DQSA consists of two pieces of legislation: Title I which is The Compounding Quality Act (CQA) and Title II the Drug Supply Chain Security Act (DSCSA). CQA creates a new entity called outsourcing facility which is much larger than the traditional compounding pharmacies and made them re-

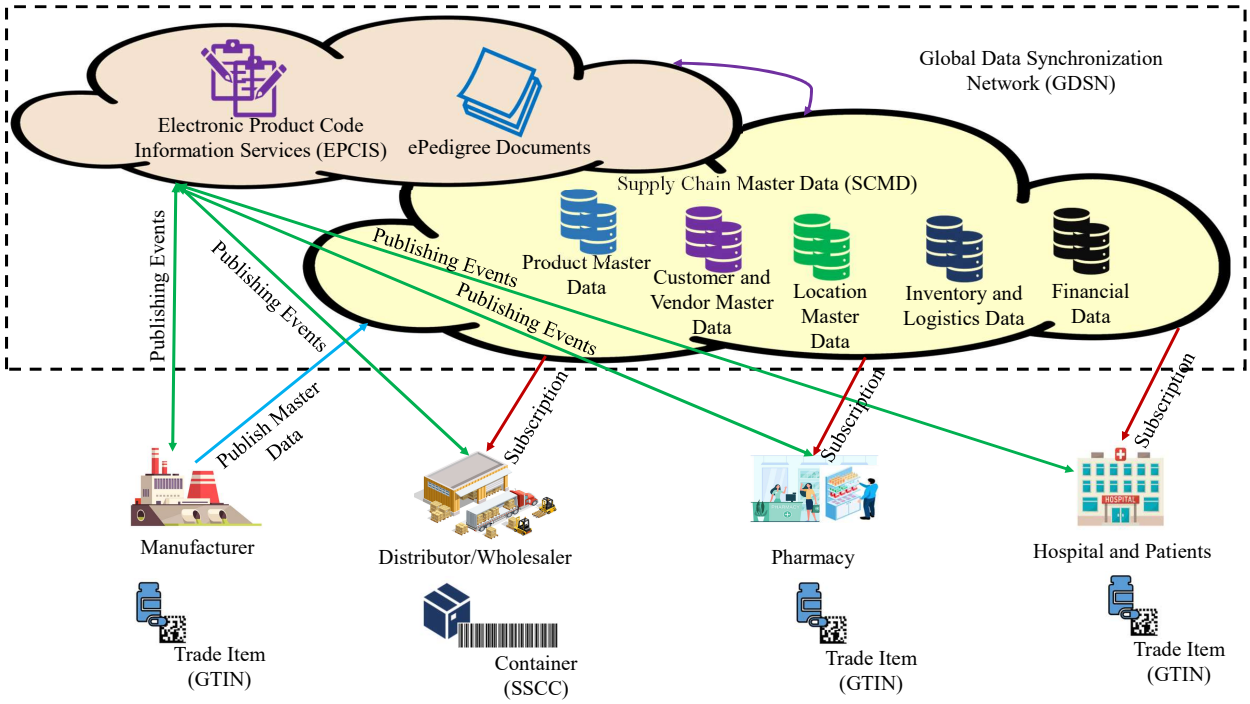

Fig. 3: Global Data Synchronization Network (GDSN) Working.

sponsible for reporting any adverse events to the FDA on all compounding drugs. These outsourcing facilities are also subjected to frequent inspections by the FDA. CQA also outlines the labeling mechanism for compound drugs. Another important aspect of DQSA is DSCSA which is formulated to prevent counterfeits, stolen or contaminated drugs from being added to the pharmaceutical supply chain. Even though DSCSA was enacted in 2013, the vision of the act is to use technological advancements to create a fully serializable pharmaceutical supply chain with full electronic operability by 2023.

2.2 Product Tracking and Tracing

Track and Trace of pharmaceutical products are defined as knowing the pinpoint past and present locations of the drugs in the supply chain. According to DSCSA, effective March 1, 2016, all the entities participating in PSC including manufacturers, distributors, re-packagers, and pharmacies must provide all the transaction history and transaction statements which is called T3 information to the subsequent product owners. T3 information helps in verifying the authenticity of the product and ensuring the drugs have been handled by the authorized trading partners and must be kept for at least 6 years after the product is received. Pedigrees are another important electronic document which is mandated by the Prescription Drug Marketing Act (PDMA) which is used to provide the entire history of drug movement within the supply chain. Pedigrees will consist of all the T3 information along with the product origin, distribution, and change of ownership. Pedigrees not only help in authenticating the product but also help in preventing drug shortages along with improving inventory management.

Tracking and tracing of the products within the supply chain needs product serialization which provides a unique identifier to each individual product. 2-dimensional barcodes are being used nowadays by manufacturers and distributors which can take more information like lot number, expiration dates of the drugs, etc. Some of the standards proposed by GS1 used in PSC are Global Location Number (GLN) which is the unique identifier given to the different entity locations like manufacturers, distributors, retail pharmacies, and health care providers. Global Trade Identification Number (GTIN) is a unique identifier that is assigned to the product passing through the supply chain and used for tracking. Serial Shipping Container Code (SSCC) is the unique identifier for the containers which are formed by grouping identical products, this unique identification is used to track the movements of containers within the supply chain. GS1 also provides standards for barcodes used in the pharmaceutical supply chain, SSCC follows a 1-dimensional barcode format GS1-128 and SGTIN fol-

lows a 2-dimensional GS1 DataMatrix format with all the information about the trade item [33]. The conceptual working of the GDSN network in tracking and tracing of the pharmaceutical supply chain is shown in Figure 3.

While this semi-centralized or centralized architecture improved the efficiency of pharmaceutical supply chains, there are still some challenges which need to be addressed. First, Integration of this with the existing systems is very difficult and also the partners in trade must also subscribe to this system. Centralized authorities are more prone to security threats and data manipulations. With increase in number of requests, the response times of the system is drastically impacted. Information fragmentation is also a major problem which doesn't provide the transparency into the supply chain which lead to many discrepancies. Auditing of such systems is also difficult and finally, cost of deployment and maintenance is too high. Hence, more alternatives has to be explored which takes benefits of latest technological advancements like Distributed Ledgers.

2.3 Distributed Ledger Technology Overview

PSCs have been evolving and becoming more efficient over time by adapting to new technological advancements. One of the recent technological advancements which have shown a significant impact is Distributed Ledger Technologies (DLT). The first successful DLT application built is Bitcoin which is a financial application to manage digital assets by solving problems of double spending and anonymity issues [22]. Along with the financial sector, DLT has shown promising solutions in various sectors like Smart Agriculture [4], Smart Healthcare [26], and Smart Transportation [17]. The bitcoin architecture has evolved over time to cater to the needs of other sectors including PSC. Bitcoin has limited scripts using which the transfer of digital assets is achieved, but a business application like smart agriculture, smart healthcare, etc. needs an entire set of Turing complete programming capabilities for developing business logic. Hence, the Ethereum platform which abstracts the complexity of the underlying blockchain architecture and provides a developer-friendly environment is designed. But both follow the blockchain data structure for storing transactions which is a linked list of blocks connected using hash pointers. This structure and other factors like consensus mechanisms have limited the throughput of the architecture. This led to exploring different types of DL data structures like IoTA Tangle, Hedera Hedge graph, etc. which can provide faster confirmation times of transactions and increased throughput.

2.3.1 Consensus Mechanism Overview

Distributed peer-to-peer networks give rise to two important problems called Byzantine Fault and Sybil Attack. Byzantine fault in distributed systems occurs when some of the nodes in the system fail or act maliciously which makes the system reach a consensus or agreement. This can lead to communication errors, data corruption, and system failure. Second, a Sybil attack is a type of security threat in a distributed system where a single malicious entity created multiple fake identities to gain control over the network and compromise the accuracy of the system. To solve these issues, a consensus mechanism is used in DLTs. A consensus mechanism is a set of rules defined and agreed upon by the entire distributed network nodes that define how the incoming transactions must be processed. Some of the most used consensus protocols are Proof-of-Work (PoW), Proof-of-Stake (PoS), Practical Byzantine Fault Tolerance (PBFT), etc. Same as the distributed ledger platforms, consensus protocols also evolved over time to be used in different applications based on their needs.

2.3.2 Smart Contracts

Smart Contracts are self-executing codes that execute automatically when certain conditions are met. This smart contract typically consists of terms of agreement and the business logic of the application and implemented on blockchain to provide secure and transparent environment for the execution. A wide variety of functions like financial transactions, supply chain management, property rights, etc. can be programmed in smart contracts and eliminate intermediaries to facilitate these transactions.

3 Related Prior Research

Apart from distributed ledgers, other technologies are also explored as solutions for addressing track and trace issues in PSC. This section is divided into two subsections which cover non-distributed ledger-based solutions and distributed ledger-based solutions both of which will discuss the state-of-art of the proposed methodologies along with their drawbacks.

3.1 Non-Distributed Ledger Solutions

Barcodes and Quick Response Codes (QR codes) are both widely used in pharmaceutical supply chains to track and trace product movement within the supply

chain. [11] build a prototype design for quality tracing of Traditional Chinese Medicines (TCM) using Two-dimensional barcodes. [32] has proposed methodologies to use QR codes combined with Web services to ensure the integrity of the products in the supply chain. Radio Frequency Identification (RFID) technology works on the principle of electromagnetic fields to automatically identify and track the physical objects to which these are attached, such as pharmaceutical products. Unlike barcodes, RFID doesn't require line of sight which removes manual intervention and automates the process of managing the inventory. [23] proposed a novel algorithm for scheduling drug delivery routes along with RFID based tracking facility and incident management mechanism. [20] has proposed a methodology where RFID can be used to maintain the integrity of the products in PSC along with addressing privacy concerns. [31] discussed the anti-counterfeit methodology using RFID event data storing and searching. A more cost-effective approach with a shorter range than RFID is Near Field Communication (NFC). NFC is used in pharmaceutical supply as a solution to prevent counterfeits which is highly valuable in high-value products like vaccines or cancer medications. Like RFID, NFC can also be used for inventory management and traceability along with temperature monitoring. Some of the proposed architectures using NFC are discussed in [3,29]. A summary of Non-Distributed based solutions are given in Table 1.

3.2 Distributed Ledger Solutions

A blockchain-based approach for drug traceability to tackle counterfeit drugs is proposed in [10, 21]. In [21] this proposed model, Lot traceability is designed by leveraging smart contracts in the Ethereum platform while logging the events on-chain. [10] along with using smart contracts and ethereum platform, also implemented SensorTag which will monitor the temperature fluctuations. Even though the proposed architectures provides a transparent blockchain, a robust access control mechanism is not implemented, and Product serialization and labeling are not discussed. The current proposed architecture includes those features and also efficiently tracks both at the lot level and item level.

Another Ethereum platform-based architecture is proposed in [12]. The proposed method concentrates on resalable returned drugs for reducing the wastage of excess quantities of drugs purchased or incorrect prescriptions. The proposed model leverages both smart contracts and off-chain storage Interplanetary Files Systems (IPFS) to handle these returned drugs. The proposed model efficiently handles the returned drugs, however, the product serialization is not discussed and no robust access control mechanisms are defined.

CryptoCargo proposed in [2] features a solution for vaccine distribution by designing an IoT-enabled container that monitors the vaccines throughout the supply chain and records the violations on blockchain to create an immutable source of truth for the stakeholders. The proposed system efficiently monitors the shipment within the supply chain; however, product serialization is not discussed. Along with that, the proposed mechanism can only track lot information, no approach is provided for item-level track and trace.

Drug Governance proposed in [1] has investigated how blockchains can be used in PSCs to reduce counterfeit drugs. A review of stakeholders of the PSC along with gaps that lead to counterfeit drugs has been investigated along with other IoT technologies which could improve the trust in the supply chain. However, no implementation or analysis is done.

PharmaChain proposed in [7] used an IoT system combined with hybrid smart contracts leveraged on the Ethereum platform. PharmaChain 3.0 application also makes use of off-chain storage to lower costs. Along with that, hybrid smart contracts are implemented combined with oracles to provide real-time shipment updates from data providers. A robust access control mechanism is also presented in this; however, the barcode mechanism or product serialization is not included, and only lot-level tracking is provided. A scalable blockchain based approach for cold supply chain using lightweight IoT-friendly Proof-of-Authentication (PoAh) consensus protocol is proposed in [5]. This approach is specifically designed for drug safety and real-time control of shipments using IoT systems.

A solution proposed in [30] uses Blockchain to store the hashes of the unique identifier assigned by the manufacturer. These unique identifiers are assigned as QR-codes to the individual units. End consumer scans the QR-codes, hashes the unique identifier received to compare with hash stored in the blockchain.

NEM blockchain-based approach is proposed in [34] which explores the design of a digital pharmacy ensuring drug safety. A comparison of state-of-art with the proposed PharmaChain 3.0 is shown in Table 2.

3.3 Problem Statement

As shown in Table 2 most of the implementations provide only lot level traceability, item/unit level traceability is required as per the guidelines of DSCSA [25]. Product serialization is another problem in PSC, current systems use centralized architecture which provides unique identities for products, managing such unique

Table 1: Summary of Non-Distributed Ledger Based Solutions for Efficient Tracking and Tracing In Pharmaceutical Supply Chain

Technology	Publication	Approach
Barcode	Cai et al. [11]	A prototype is designed based on two-dimensional barcode and web server. It is a centralized architecture designed for tracking and tracing of Traditional Chinese Medicine (TCM). A mobile app is designed which can retrieve TCM quality and chemical fingerprints.
	Shaik et al. [32]	An architecture utilizing the Public Key Infrastructure (PKI) system, barcodes and web services to develop anti-counterfeit mechanism for different products. In this each manufacturer is assigned with public-private key pair and every product produced by that manufacturer will be assigned with a QR code which has encrypted product identification code. Public key is made available to everyone to check the authenticity.
RFID	Onieva et al. [23]	Proposed approach uses RFID tags for real-time incident reporting while drugs are moved using 3PL. It uses On-board system which is equipped with RFID reader, GPS Module, Mobile application which are communicated using different communication technologies like Bluetooth and Wi-Fi to provide real-time tracking and tracing along with incident reporting.
	King et al. [20]	This approach discusses the necessary requirements for ensuring the product authenticity in Pharmaceutical Supply Chain using RFID technology while ensuring the necessary information is accessible to the regulatory agencies.
	Schapranow et al. [31]	Discusses the RFID based software architecture for counterfeit resistant pharmaceutical supply chain. It also provides a quantitative approach to analyze efficient way of searching RFID events.
NFC	Alzahrani et al. [3]	It proposes a Tag Reapplication Detection (TRD) for avoiding duplication of NFC tags for securing Pharmaceutical Products. It utilizes one-time scan NFC tags which can be utilized to retrieve information only once. This avoids duplication of NFC tags and introducing counterfeit drugs.
	Saeed et al. [29]	This approach combines NFC Tags and Public Key Infrastructure (PKI) system to offer dual layer authentication. It equips consumers with both visual and cryptography proofs to verify authentic products.

identities on the blockchain is difficult and can be easily duplicated to introduce counterfeits. PharmaChain 3.0 utilizes smart contract addresses as unique identities both for lots and products which also avoids different issues with such semi-centralized architectures like GDSN. It also facilitates following the standards like GS1 which can help in achieving compliance with DQSA and pedigree. Along with these, PharmaChain 3.0 provides an easy way of labeling products and lots thereby providing easy track and trace. Along with these, PharmaChain 3.0 also aims to include robust smart contract-based Role-Based Access Control (RBAC) to define different entity roles along with controlling the access to different smart contract functions.

4 Novel Contributions of this Paper

This section discussed the problems faced in traditional PSCs and novel solutions proposed in PharmaChain 3.0 blockchain-based architecture with integrated product serialization.

4.1 Problems Addressed in Current Paper

Problems addressed in PSC are:

- Removing the centralized authorities like Enterprise Resource Planning Systems (ERPs) in PSCs removes the blind parties and enhances transparency and security.

Table 2: Comparison between state-of-art with proposed PharmaChain 3.0

Works	Platform	Consensus Protocol	Storage	Large data handling	Lot Level Traceability	Item level traceability	Access control mechanism	Product Serialization (Digital-twin)	DSCSA Compliance
Musamih et al. [21]	Ethereum	Proof-of-Work (PoW)	On-chain and off-chain	✓	✓	✗	✗	✗	✗
Bocek et al. [10]	Ethereum	Proof-of-Work (PoW)	On-chain	✗	✓	✗	✗	✗	✗
Debe et al. [12]	Ethereum	Proof-of-Work (PoW)	On-chain and off-chain	✓	✗	✗	✗	✗	✗
Alkhoori et al. [2]	Ethereum	Proof-of-Work (PoW)	On-chain and off-chain	✗	✓	✗	✗	✗	✗
Ahmadi et al. [1]	NA	NA	NA	NA	✓	✗	✗	✗	✗
Subramnian et al. [34]	NEM	Proof-of-Importance (PoI)	On-chain	✗	✓	✗	✓	✗	✗
Saindane et al. [30]	NA	NA	On-Chain	✗	✗	✓	✗	✗	✗
PharmaChain [7]	Ethereum	Proof-of-Authority (PoA)	On-chain and off-chain	✓	✓	✗	✓	✗	✗
PharmaChain 2.0 [5]	EasyChain [8]	Proof-of-Authentication (PoAh)	On-chain	✗	✓	✗	✓	✗	✗
PharmaChain 3.0 (Current)	Ethereum	Proof-of-Stake (PoS)	On-chain and off-chain	✓	✓	✓	✓	✓	✓

– Efficient way of identifying and avoiding counterfeit drugs in the PSC to increase drug safety and strengthen belief in healthcare systems.
– Transparent supply chain makes it easy to identify and penalize the adversaries acting in the supply chain network.
– Reducing financial loss for both patients and companies by avoiding counterfeit medications in PSC.
– Cost of product serialization is high and is maintained by centralized or semi-centralized systems. It is reduced in the proposed PharmaChain 3.0.
– Response times of such centralized systems are higher and based on the number of transactions processing at that time. The decentralized system proposed in PharmaChain 3.0 can provide better response rates.
– Data fragmentation issue with the PSC is addressed by providing a single source of truth distributed ledger.
– Integration and adaptation of these serialization systems require all the trading partners to be subscribed to the same service provider. The solution proposed in PharmaChain 3.0 can address this issue.

4.2 Novel Solutions Proposed in PharmaChain 3.0

Below are the novel solutions proposed in current PharmaChain 3.0:

- Peer-to-Peer (P2P) network and processing the transaction based on consensus protocol removes the need for centralized authorities to facilitate transactions.
- In the DLT application PharmaChain 3.0, the distributed ledger is copied and updated at each and every participating entity node which helps in creating a single source of truth. Thereby, creating a transparent supply chain with no blind parties.
- As all the transactions are logged in the immutable ledger, it is easy to identify the adversaries who are trying to introduce the counterfeits and penalize them which is difficult in traditional PSC.
- Shared ledger proposed in PharmaChain 3.0 provides high availability and low latency for information retrieval about drugs.
- Cost of product serialization is reduced by using the smart contract addresses as the unique identities for both products and lots.
- Identifying the counterfeits is easier with a single scan of the Barcode which reduces unnecessary costs for both patients and companies.
- Information related to medicines like usage instructions, warnings, side effects, etc. which have large amounts of data can be uploaded to IPFS in proposed PharmaChain 3.0 and make available for consumers with a single Barcode scan.
- Unit level tracing provided by PharmaChain 3.0 can help reduce a lot of wastage during recalls and more control over products within the supply chain.

5 Architecture Overview of the Proposed PharmaChain 3.0

An architectural overview of the proposed PharmaChain 3.0 is shown in Figure 4 and the detailed interactions between different actors is clearly shown in sequence diagram Figure 5. The main components of the proposed architecture are: First, entities of the PSC which include manufacturers, retailers or wholesalers, pharmacies or healthcare units, and patients. The manufacturer is responsible for conducting research and development of new drugs along with getting required approvals from regulatory agencies for producing and marketing the drugs. The manufacturer is also responsible for product serialization and giving unique identities to each unit and lot produced. The distributor or Wholesaler buys lots from the manufacturer at Wholesale Acquisition Price (WAP) and sends them to the pharmacies and healthcare units through which patients can access the drugs. Apart from these, there will be regulatory bodies like the U.S. Food and Drug Administration (FDA) which monitors and activities on the whole supply chain interactions.

Second, the Blockchain layer consists of Peer-to-Peer nodes which are deployed and maintained by all the entities participating in the network. As drugs are within the supply chain, each acting node will handle the drugs and create an event that will be published to the P2P network as blockchain transactions. These transaction events will be processed and recorded on the immutable ledger which is copied at each participating node. This replicated ledger at each node will act as the single source of truth and increase transparency among the distributed entities. Proposed PharmaChain 3.0 makes use of the Ethereum platform for creating and managing the ledgers. The consensus protocol used in Ethereum was Proof-of-Work (PoW) and recently shifted to Proof-of-Stake (PoS) since Ethereum 2.0 upgrade to reduce energy consumption. Unlike miners in PoW, PoS will have validators who lock up a certain amount of ether as a stake. Validators to propose a new block is chosen based on the amount of ether staked. As PoS doesn't depend on high computational cryptography problems, energy consumption is less compared to PoW. The Ethereum environment is analogous to a single-world computer called Ethereum Virtual Machine (EVM) which consists of deployed smart contracts. EVM provides a secure environment for the execution of smart contracts and ensures it is deterministic across all the nodes participating in the P2P network. It operates on the principle of gas. Gas is a unit of measure for the computational effort required for performing smart contract functions and it depends on the complexity of the operation. Due to its smart contract functionality and ease of creating Decentralized Applications (DApps) along with its diverse ecosystem and developer community Ethereum has been most widely accepted. Hence, the same is adopted in PharmaChain 3.0.

Third, Off-chain storage layer, as discussed above the gas cost is associated with the number of computations and as the amount of data being stored on-chain increases, it will increase the gas cost. To avoid large on-chain storage, off-chain storage is used which will reduce the operational costs of the application. Inter Planetary File System (IPFS) is used in PharmaChain 3.0. IPFS is a distributed network of nodes that stores and shares data. Unlike web protocols where data is location-based access using Uniform Resource Locator (URLs), IPFS uses content-based addressing which uses unique cryptography hashes. Whenever a new file is added to IPFS,

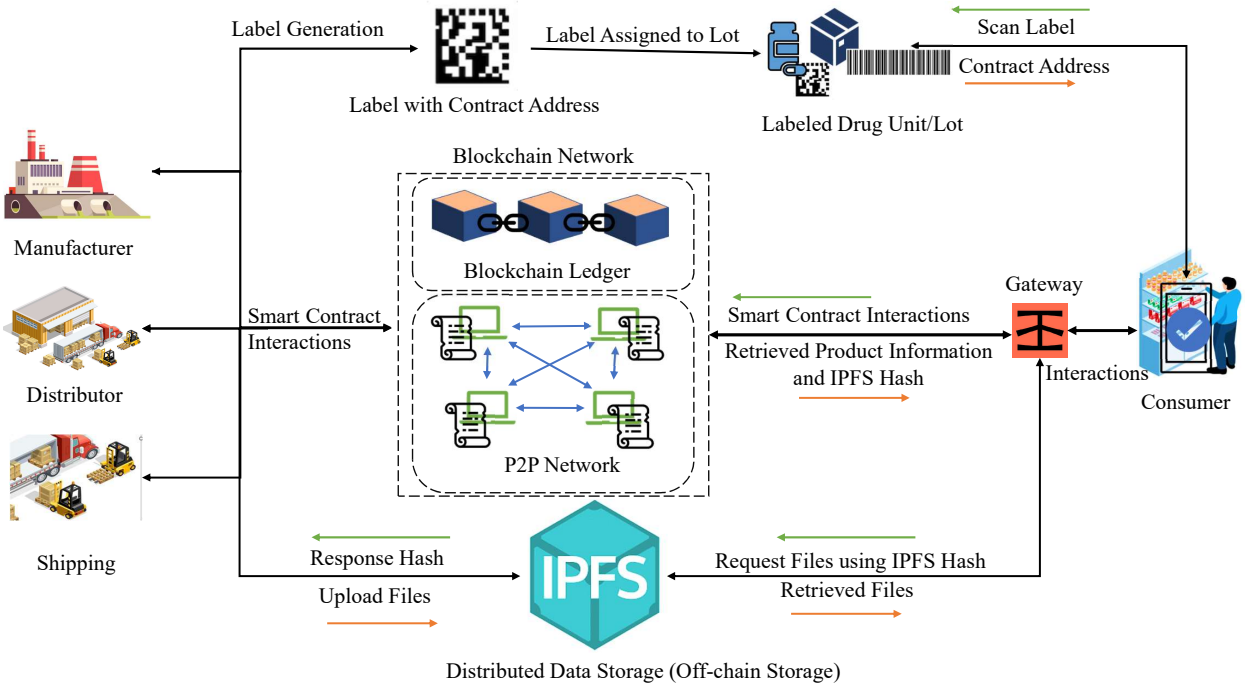

Fig. 4: Architecture Overview of Proposed PharmaChain 3.0.

it will be divided into smaller blocks and each block is hashed to get a unique content hash. These blocks assigned with a unique content hash will be distributed across all the nodes in the network. These blocks are organized and managed in Merkle Directed Acyclic Graph (Merkle DAG) which makes it tamper-proof and facilitates efficient verification and retrieval of data. Retrieval of files from IPFS makes use of Distributed Hash Tables (DHT), whenever a request comes to the IPFS network, based on the requested File Content ID (CID) the node which stored the files is looked up from DHT. IPFS also implements caching mechanisms to provide faster access to frequently fetching file contents.

Fourth, the Ethereum gateway layer helps in interacting with Ethereum network Application Program Interfaces (APIs) without needing to run their own node and participate in the P2P network. This provides a simplified interface for interacting with Ethereum abstracting the complexity of deploying and managing Ethereum nodes by DApp clients. Infura service is used in PharmaChain 3.0. Endpoint APIs provided by Infura will help in performing Ethereum transactions along with querying blockchain data and interacting with deployed smart contracts. It also makes it easy to integrate blockchain technology into web3 and create highly responsive user interfaces (UI).

Finally, the client layer will scan the data matrix and GS1-128 barcodes to fetch smart contract addresses. It will facilitate interactions with smart contracts through Infura APIs. Entities participating in the network will be able to use this client program and fetch all the drug information both from ledger data and IPFS file contents.

5.1 Proposed Algorithms for PharmaChain 3.0

Interactions of the manufacturer in PharmaChain 3.0 architecture are clearly shown in Figure 6. Before starting to manufacture the drugs, the manufacturer or Market Authorization Holder will upload to IPFS all the information about the drugs which is intended for the public to ensure patient safety. One of the most important documents includes a Package insert or Patient Information Leaflet (PIL) which will have important information about the composition of the drug, use of the drug, dosage instructions, side effect warnings, and precautions. Another important document is the Summary of Product Characteristics (SmPC) which includes comprehensive information on drugs which are needed by healthcare professionals before prescribing them to patients. Once all these files are uploaded into IPFS, Content ID (CIDs) returned will be noted by the manufacturer. Whenever a unit of the drug is produced, the Unit contract is invoked with information from a manufacturer like a name, address, contact information, and manufacturing date. Along with these, CIDs from IPFS uploads will also be updated to the unit contract

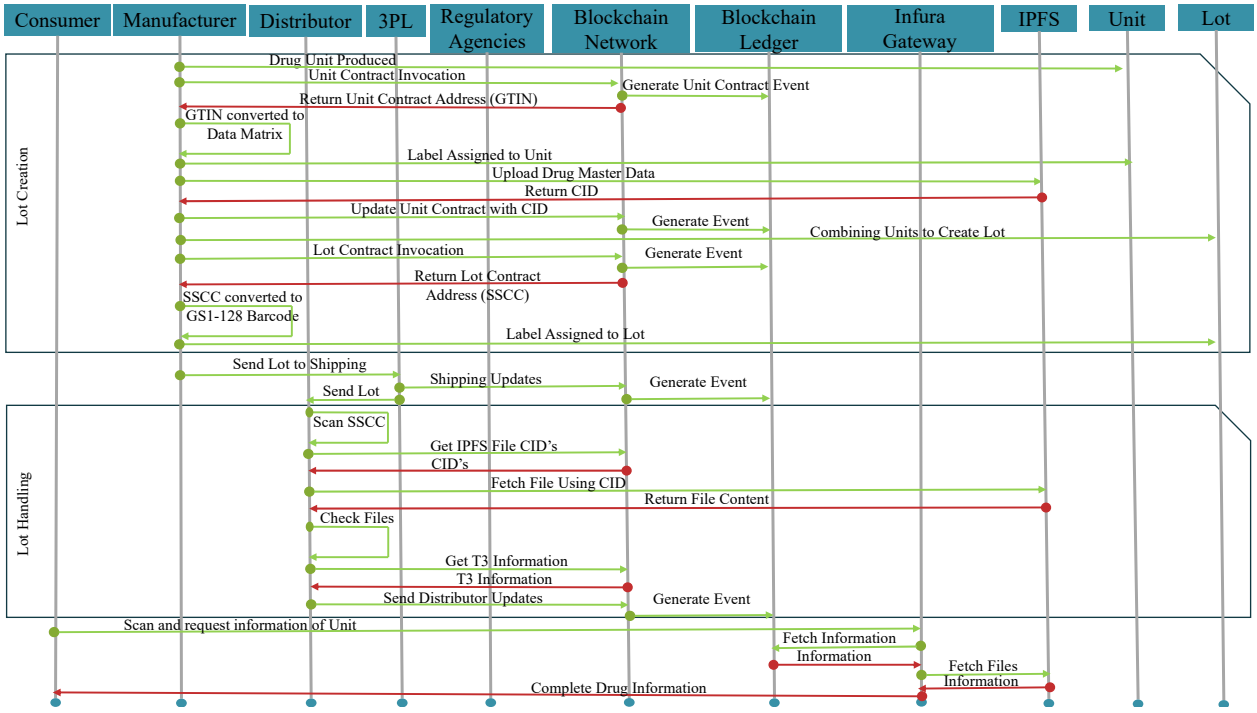

Fig. 5: Sequence Diagram of Proposed PharmaChain 3.0.

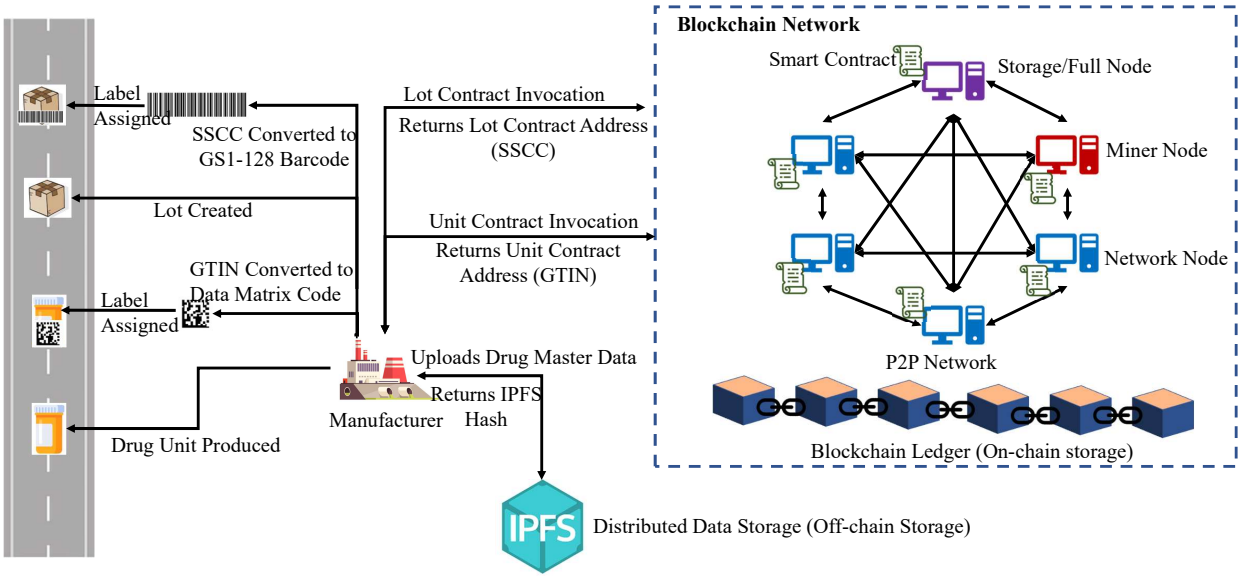

Fig. 6: Manufacture Interaction in Proposed PharmaChain 3.0 Architecture.

created for each unit produced. Returned unit contract address is considered a GTIN number which is used for tracking and tracing individual drug units. These unit contract addresses are embedded into Data Matrix 2D barcode which is easily printed onto individual unit packages. The manufacturer ships the drugs to wholesalers or retailers in lots which is a group of individual units. Before shipping, the manufacturer invokes the lot contract and aggregates individual units into the lot. Created lot contract address is also updated to individual assigned unit contracts. The returned lot contract address acts as the SSCC and is converted to 1D barcode which will be appended to the lot. Once the lots are created, those will be moved to the wholesaler using third-party logistics or transport managed by the manufacturer.

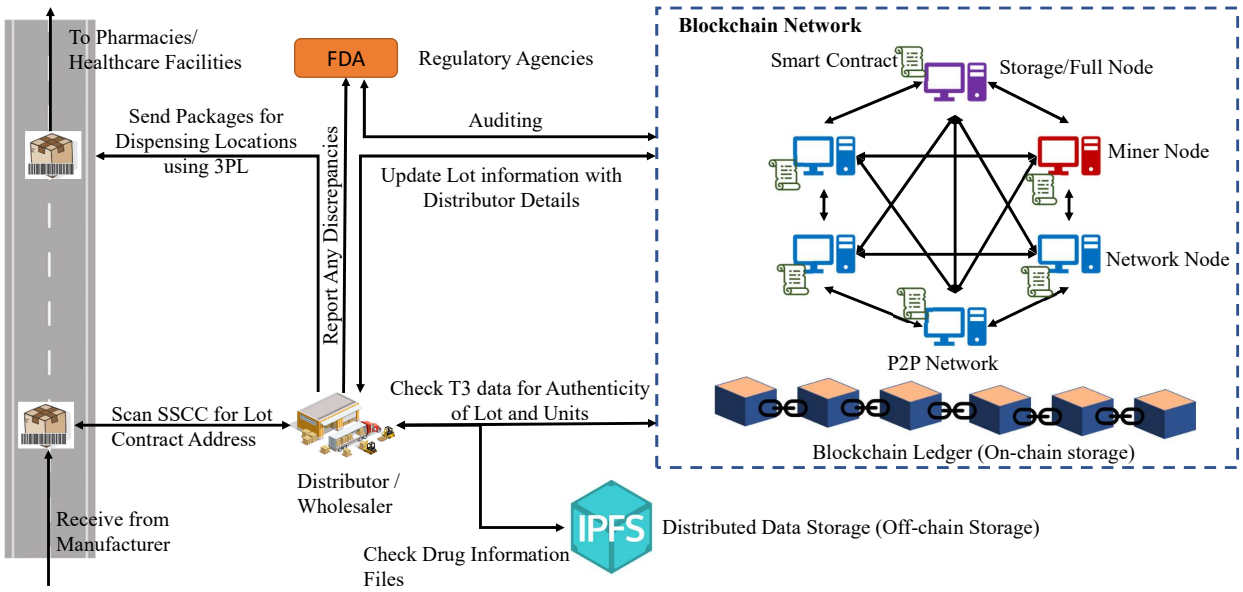

Fig. 7: Distributor Interaction in Proposed PharmaChain 3.0 Architecture.

A series of steps in the manufacturer interaction and creating lots is clearly shown in Algorithm 1.

Interactions from the Distributor or Wholesaler is clearly shown in Figure 7. To verify the ePedigree of the received lot, the wholesaler will scan the SSCC 1D barcode printed on a lot to get the lot contract address. From the lot contract, required details about the drug from previous manufacturer transactions along with IPFS files are verified. As per policies, a certain percentage of the units within the lot also should be verified for authenticity. For doing that, the wholesaler will unpack the lot and scan some of the data matrix printed on individual units to fetch individual unit contract addresses through which required information can be verified. If any discrepancies are found, they will be reported to the regulatory agencies. Otherwise, the lot contract is updated with the distributor or wholesaler information along with handling instructions. After that, packaged lots are sent to the healthcare units, and pharmacies for further reach to patients. Sequential steps are shown clearly in Algorithm 2.

Like these entities, healthcare units or pharmacies will also process the lots and units while verifying the chain of custody through ePedigree documents. This ensures the authenticity of the drugs reaching the patients. Patients can also run the client program which is used to retrieve unit-level logs and check the trail of drugs through the supply chain. The user who wants to check the authenticity of the product scans the Data Matrix barcode on the unit package to get the unit contract address. Infura provides an easy and reliable way to interact with the blockchain network without need for deploying and maintaining own node. This simplifies the process of accessing information by the end consumer. Once the unit contract address is obtained, request is sent to Infura endpoint for accessing drug usage information files. Infura retrieves IPFS hashes of the uploaded drug information files. With the help of these hashes, the data files are accessed which will have the PIL and other necessary documents. Along with this, the trail information stored on-chain is retrieved to verify the entire trail of drugs in the supply chain. Sequential steps involved in patient actions are shown in Algorithm 3.

6 Implementation of the Proposed PharmaChain 3.0

6.1 Smart Contract Design

The design of smart contracts should be very efficient and secure as the entire business logic of the DApp is embedded into the smart contracts. There are some established design patterns that are already tried and efficiently wo rking in ot her ap plications, an d it is a good idea to follow such design patterns to avoid costly errors. There are many categories of design patterns among which factory pattern comes under contract management patterns. As in the proposed PharmaChain 3.0 application contract addresses serve as the product serialization identities like GTIN and SSCC, and there will be many contracts that have to be managed. Hence, fol-

Algorithm 1: Product Serialization and Manufacturer Interaction in Proposed PharmaChain 3.0

Data: Newly manufactured drug information files, CID, manufacturing date, expiry date, manufacturer details
Result: GTIN for drug unit traceability and SSCC for lot created

for *Each drug file* **do**
  Upload each individual file on IPFS;
  $\text{IPFSHash}_{file} \leftarrow$ IPFS.add(File);
  Returned hash is then noted by manufacturer;
end
for *Each drug unit produced* **do**
  New unit contract is created by calling the paernt contract;
  $\text{Contract}_{unit} \leftarrow \text{Contract}_{partent}$.createNewUnitContract();
  Update the drug file hashes from IPFS to unit contract;
  Contract_{unit}.addIPFSHash(IPFSHash_{file});
  Add all the information about manufacturer, manufacturing date, expiry date;
  Contract_{unit}.addDrugDetails(Manufacturer Information, Manufacturer and Expiry date);
  Create a DataMatrix 2D barcode with newly created unit contract address information;
  Label.embed(Address(Contract_{unit}));
  Print the generated DataMatric 2D Barcode on each unit packages;
end
Creating drug lot before shipping;
for *Drug lot created* **do**
  Lot specific contract is created by calling parent contract;
  $\text{Contract}_{lot} \leftarrow \text{Contract}_{partent}$.createNewLotContract();
  Add individual units to the lots;
  Contract_{lot}.addUnits(unit contract addresses);
  Create a 1D barcode with drug lot contract address which acts as SSCC;
  Label.embed(Address(Contract_{lot}));
  Print the generated 1D barcode on to the lots created.
end

Algorithm 2: Lot Handling and Wholesaler Interaction in Proposed PharmaChain 3.0

Data: Received lot with SSCC 1D barcode, Distributor information, Handling instructions
Result: Track and Trace updates

for *Each drug lot received* **do**
  Entity scans the 1D barcode to retrieve the lot contract address;
  $\text{Contract}_{lot} \leftarrow$ barcodeScan();
  Retreive lot information to verify the ePedigree;
  ePedigree $\leftarrow \text{Contract}_{lot}$.retreiveLotInfo();
  if *Verified* **then**
    Unpack the lot to verify percentage of units;
    for *Each individual unit* **do**
      Entity scans the Data Matrix 2D barcode and get unit contract adress;
      $\text{Contract}_{unit} \leftarrow$ barcodeScan();
      Retreive unit information to verify authenticity;
      Unit information $\leftarrow \text{Contract}_{unit}$.retreiveUnitInfo();
      if *Units verfified* **then**
        Update the ditributor or wholesaler information;
        Contract_{lot}.addWholesalerInfo();
      end
      else
        Report discrepencies to regulatory authorities;
      end
    end
  end
  else
    Report discrepencies to regulatory authorities;
  end
end

lowing such an established factory smart contract pattern is a best practice.

Factory pattern is used to create the smart contracts dynamically and allows abstracting the object creation by providing a centralized factory contract that handles the creation of new contract instances. Using this pattern increases the code re-usability, modularity, and flexibility in managing the contract instances. In this pattern, there will be a concrete factory contract that is responsible for creating instances of the product contracts based on passed parameters. This concrete factory will also have additional logic for the functionality of interacting and managing the created product instances. The designed PharmaChain 3.0 smart contracts same approach and has the contract 'SupplyChain.sol' which is a concrete factory contract with product contracts as 'Unit.sol' and 'Lot.sol'. Class diagram of the implemented 'SupplyChain.sol' is shown in Figure 8. The class diagram visualizes the contract structure along with the association between different contracts.

Role-based access control (RBAC) mechanism is implemented in PharmaChain 3.0 which helps in providing a granular level of control and allows specific roles to be defined and assigned to different individuals. Based on the roles assigned, corresponding privileges can be defined and enforced for users. RBAC is very important in the PSC management system.

- Access control ensures only the authorized entities can perform only assigned actions. This helps in prevention of unintended actions in the network.
- Product information, pricing and other sensitive information should be secure and shouldn't be modified by unauthorized entities. RBAC provides such data security in implemented smart contracts.

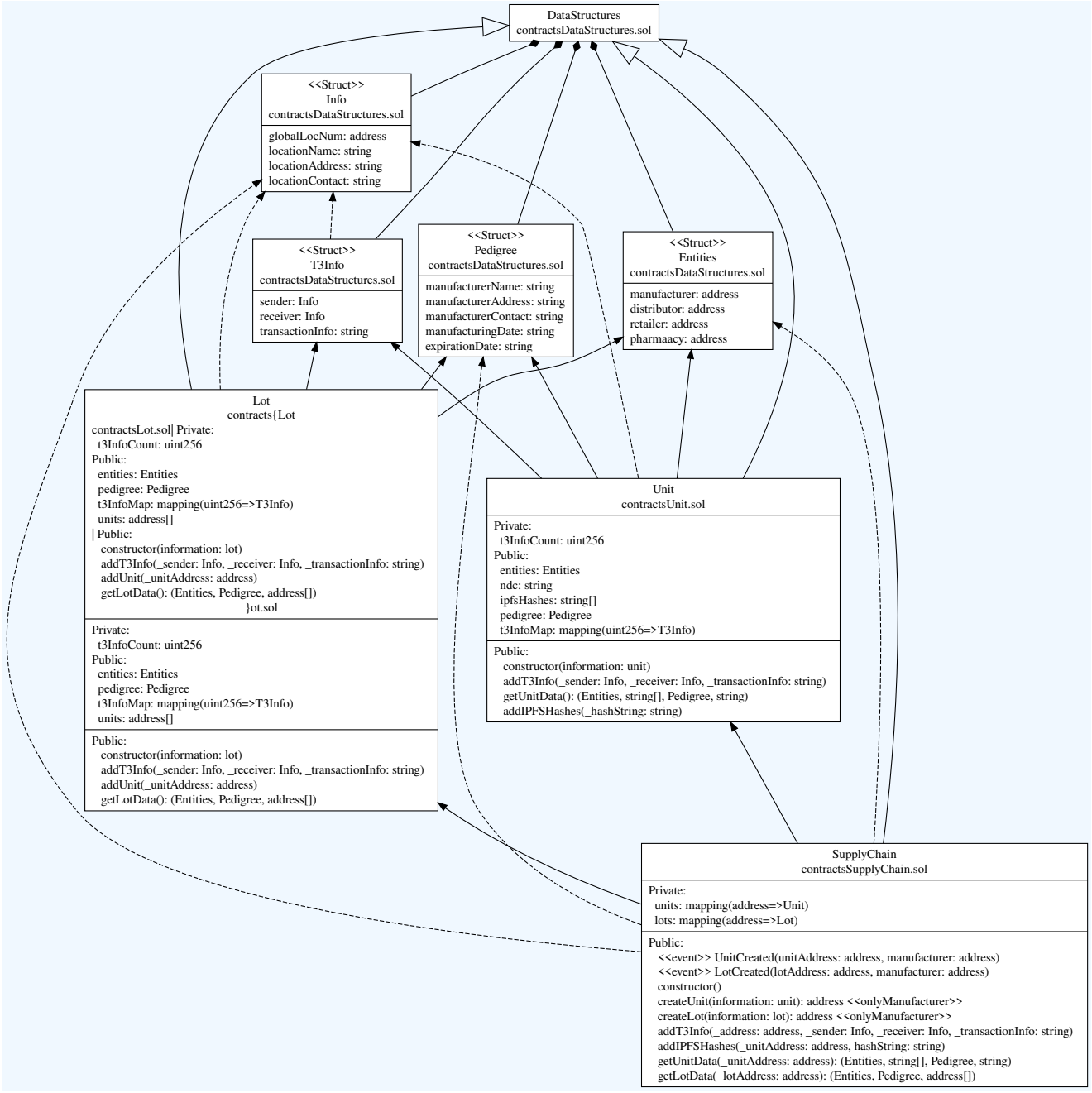

Fig. 8: Implemented Supply Chain Smart Contract UML Class Diagram for Proposed PharmaChain 3.0

– Compliance and auditability can be improved by implementing RBAC in pharmaceutical supply chain smart contracts which can also provide trail of who performed which action and what data is accessed.
– Process management within the supply chain can also be improved by implementing RBAC system.
– Having separate RBAC implemented can help increase the scalability and flexibility in the system by allowing addition and management of new roles without affecting the whole system.

Class diagram of implemented smart contracts for RBAC in PharmaChain 3.0 is clearly shown in Figure 9.

Truffle suite is used to develop these smart contracts. Truffle is a development environment framework for developing Ethereum DApp and it simplifies the development process and designing of smart contracts. As part of the development suite, truffle also provides Ganache which is a development blockchain that emulates the Ethereum environment for testing purposes lo-

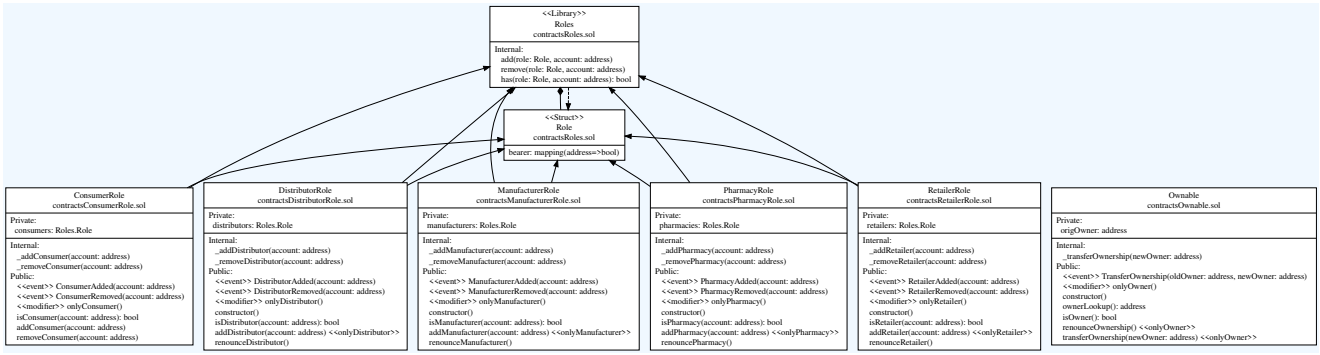

Fig. 9: Implemented Role Based Access Control (RBAC) Smart Contract UML Class Diagram for Proposed PharmaChain 3.0

Algorithm 3: Drug Information Access and Product Authenticity Verification in Proposed PharmaChain 3.0

Data: GTIN from Data Matrix printed on unit package
Result: Authenticity of the product and PIL information

1 User scans the Data Matrix barcode to get the unit contract address;
2 $\text{Contract}_{unit} \leftarrow$ barcodeScan();
3 Send retrieve request to Infura endpoint with unit contract address as parameter;
4 Infura node will query the blockchain and get IPFS hashes;
5 IPFS hashes are retrieved from the unit contract call;
6 $\text{IPFSHash}_{file} \leftarrow \text{Infura.Contract}_{unit}\text{.getHashes}()$;
7 **for** *Each IPFS Hash* **do**
8 | Retrieve each information file;
9 | DrugUsageInformation $\leftarrow$ IPFS.get(IPFSHash_{file});
10 **end**
11 Send trail information request to the Infura endpoint;
12 To verify authenticity, check the entities information updated in the smart contract;
13 TrailInformation $\leftarrow$ $\text{Infura.Contract}_{unit}$.getTrailInfromation();
14 Authenticity of product can be checked along with all required drug information can be accessed;

cally. It provides 10 free accounts which are pre-funded with 100 test ETH for testing purposes. This development suite is chosen as it is easier to develop and test the intended application with easier configuration and abstracting complexity of hosting the own test network. Leveraged Ganache blockchain with provided test accounts is shown in Figure 10. MetaMask wallet browser extension is used to connect to the accounts provided by Ganache and make any transactions.

For distributed data off-chain storage, Interplanetary File System (IPFS) is used in PharmaChain 3.0. IPFS provides many advantages like decentralization, content-based addressing, Data integrity and security,

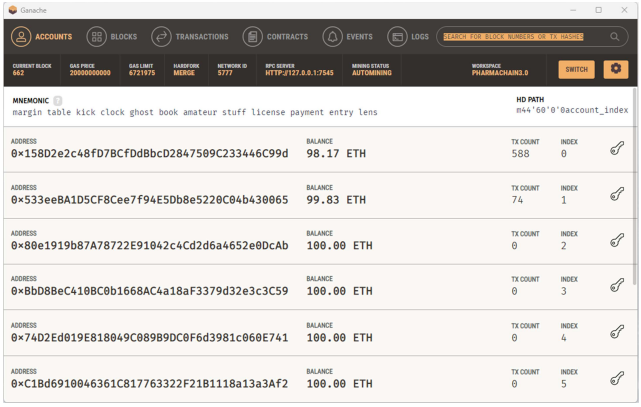

Fig. 10: Leveraged Ganache Blockchain with provided Test Accounts in implemented PharmaChain 3.0

ease of integration to the designed DApp, etc. Considering all these advantages, IPFS is chosen as decentralized data storage for PharmaChain 3.0. A simple UI is designed for implementing PharmaChain 3.0 using JavaScript, Web3.js library, HTML, and CSS. The designed UI is shown in Figure 11.

Table 3 provides information on all the software setup along with the versions used.

7 Experimental Results

7.1 Functional Validation of Implemented PharmaChain 3.0

This subsection discusses the functional validation of the implemented PharmaChain 3.0. Truffle suite also provides a built-in testing framework to help write and execute the test cases for solidity smart contracts. This testing framework is built on Mocha and Chai which are JavaScript libraries and provides a variety of assertion methods to verify the results. As most of the smart

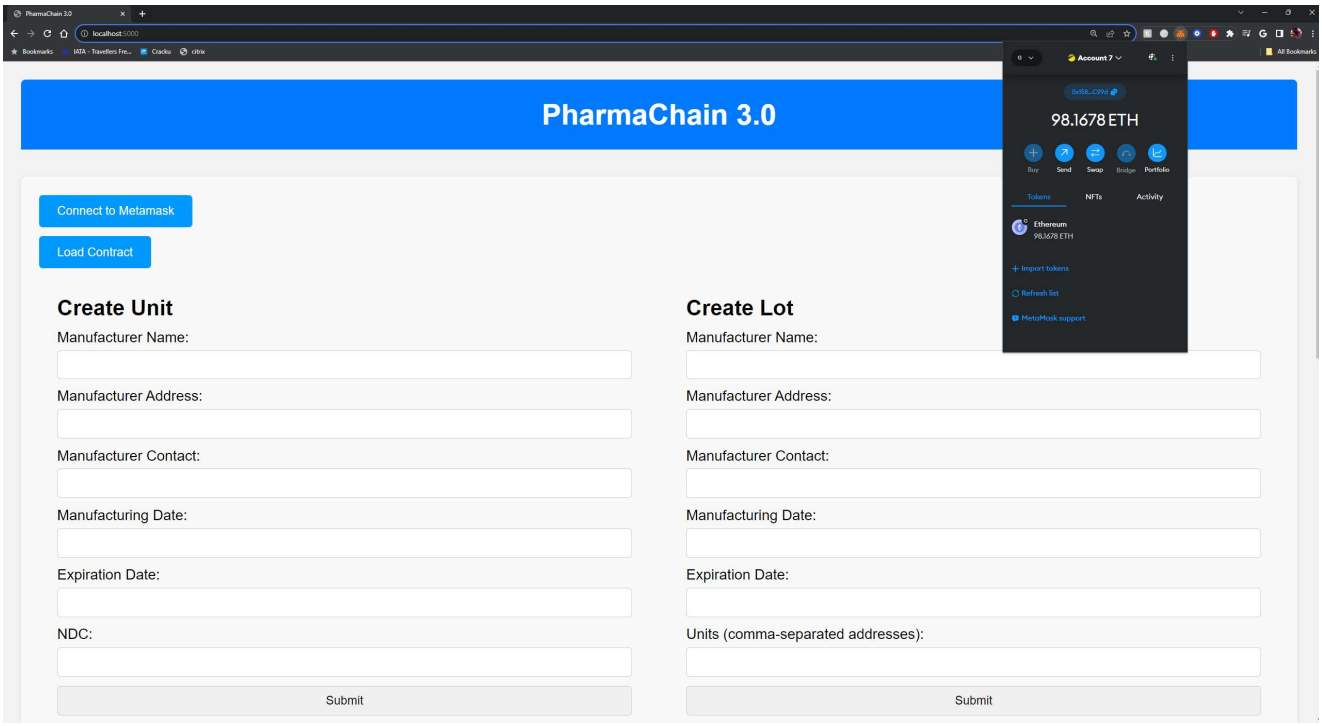

Fig. 11: User Interface with Manufacturer View Of Implemented PharmaChain 3.0

Table 3: Software Tools and Version in Implemented PharmaChain 3.0

Tools	Version
Truffle Suite	5.4.28 (core: 5.4.28)
Ganache Blockchain	2.7.1
Solidity Compiler	0.8.11 (solc-js)
MetaMask	10.31.1
Node	16.13.1
Web3.js	1.5.3
Express framework	4.18.2

Fig. 12: Testing Implemented Smart Contracts Using Truffle Suite in Implemented PharmaChain 3.0.

contract interactions are asynchronous, it also supports async/await syntax while writing test cases. A series of test cases are written on the implemented smart contracts for PharmaChain 3.0 which include proper role assignment and revocation, unit/lot creations, and adding and accessing the T3 information. Results from the test cases execution can be seen in figure 12.

Test accounts provided by the Ganache blockchain are used for testing purposes. Used test accounts along with their assigned roles while testing is shown in Table 4.

Generated GTIN for the unit created and SSCC for the lot created can be seen in Figure 13.

Table 4: Test Accounts and Assigned Roles in Implemented PharmaChain 3.0

Account Address	Role
0x158D2e2c48fD7BCfDdBbcD2847509C233446C99d	Contract Owner
0x533eeBA1D5CF8Cee7f94E5Db8e5220C04b430065	Manufacturer
0x80e1919b87A78722E91042c4Cd2d6a4652e0DcAb	Distributor
0xBbD8BeC410BC0b1668AC4a18aF3379d32e3c3C59	Retailer
0x74D2Ed019E818049C089B9DC0F6d3981c060E741	Pharmacy
0x6e2A301ab529f9a74B0C1E29B4815a49a9feB030	Deployed Supply-Chain contract
0x2f852476CA42280977eA8D193b831A6E158d9C43	Created Unit contract
0x4243FD54575c6543f0541d92aed8C08Cc5153E91	Created Lot contract

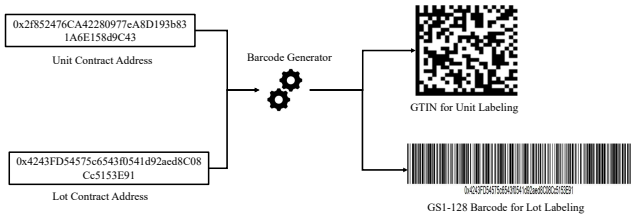

Fig. 13: Generated GTIN and SSCC for Unit and Lot created in Implemented PharmaChain 3.0

7.2 Product Serialization Uniqueness

As millions of units are produced daily across the world, product serialization should provide unique identities to each, and every unit or lot produced. Any collision between these identities can cause serious issues in tracking and tracing within the supply chain. As each contract is created every time and the contract address is used as a serialization identity in PharmaChain 3.0, it is required to evaluate whether such collisions happen or not. Such analysis is done in this sub-section. Ethereum Externally Owned Accounts (EOA) is represented by using a 42-character hexadecimal string, EOA contains both individual account addresses and contract addresses. Among these 42 hex characters, two characters are prefixed '0x' which indicates the address is in hexadecimal format. The remaining 40 characters serve as the address which is a combination of uppercase A-F and digits 0-9. The total address space for Ethereum can be calculated as:

$$2^{160} = 1.46 \times 10^{48} unique addresses$$

As we can see the number of unique addresses is astronomically large which makes it unlikely to have collision in unit or lot contract addresses.

7.3 Security Analysis

Blockchain platform provide many security features which has enhanced the security of designed PharmaChain 3.0 application. This subsections provides a comprehensive analysis of the proposed system's security.

Access Control and Authorization: Pharmaceutical Supply Chains are complex with a large number of entities interacting in complex ways. Hence, there is a need for an access control mechanism to ensure the entities can perform only the assigned functions. A robust access control mechanism is implemented using smart contracts in PharmaChain 3.0. An immutable log is also generated whenever new roles are created, assigned, or revoked which helps in the auditability of the system.

Accountability and Non-Repudiation: Every transaction performed by the entities has to be digitally signed by the entities before sending it to the network. Any adversary participating in the network will not be able to generate any false transaction without having the private key of the entities. This also ensures the accountability of each participating entity as it is easy to find out if any of the participants are trying to introduce false information into the network and take necessary steps like reporting it to the regulatory authorities.

Data Security: All the transactions performed in the blockchain once added to the blocks are immutable. As both state and blockchain are copied to all the participating nodes in the network, it will make it nearly impossible for the adversary to make any modifications to a confirmed transaction.

Data Availability: As the proposed PharmaChain 3.0 is a decentralized system and updates are processed based on the consensus mechanism, it is robust to node failures and keeps the network active even when some of the nodes are unresponsive/malicious.

Sybil Attack: Sybil attack is one of the threats in a P2P network where adversaries create multiple fake identities to gain control over the network. Identity verification is one of the efficient mitigation techniques for a Sybil attack. PharmaChain 3.0 makes use of public keys and assigns different roles to the entities. This

Table 5: Cost and Time Analysis of Implemented PharmaChain 3.0 on Sepolia Testnet

Function	**Estimated Gas** ($> 30sec$)	**Estimated Gas** ($< 30sec$)	**Estimated Gas** ($< 15sec$)	**Actual Transaction Fee (ETH)**	**Transaction Hash**
Contract deployment	0.00502418	0.00753627	0.01004836	0.012560	0xc9dda55f9c27e58293bb 43b76ddd29293ead9367ca 9b8b2010cff1e896dd1651
Adding Manufacturer	0.00004793	0.0000719	0.00009586	0.0001198	0xf8c5489f27ebbf3476e7 d41986c33b739ddffc8a199 b60187d95bcaf4d4242a7
Adding Distributor	0.00004789	0.00007183	0.00009577	0.0001197	0x2ca68a939fffb89969df89 832293622676af37e6ed1e 8cee34bafa3df597cf51
Adding Retailer	0.00004791	0.00007186	0.00009582	0.0001197	0x474fcbf02fba91a79cc8ce 9b6af8124a46b0f91966d83 037c6616cb4b16cce3a
Creating Unit	0.00154876	0.00232315	0.00309753	0.0038710	0xc1355164080480ba4fe47 910cca7375078acf30c26025 4e8d3c18f028c1e1787
Adding IPFS Hashes	0.0000767	0.00011504	0.00015339	0.0001900	0x8984934415b23b7e9a7cf 12f293ce44a4e497f1b4f220 6e06ee477def5ce94a1
Creating Lot	0.00147323	0.00220985	0.00294646	0.0036830	0x7fb7b5cfa16214e565644 81a3e3d5e290edf2c944c77 182c84f38ccbdd0f27b
Adding T3 Information	0.0002775	0.00041625	0.000555	0.0006846	0xc5817fa0aa66f4bc3aa25 ea8e7d7ec5a6785173f8d67 845516959410b74114d9

robust access control mechanism ensures only transactions from valid nodes are processed avoiding fake identities.

7.4 Evaluation Metrics

7.4.1 Gas Consumption

In Ethereum Blockchain platform the cost of computational and storage instructions are measured using 'gas'. This is measured in 'gwei' which is the smallest denomination of the Ethereum native currency Ether (ETH). Total cost of an operation is computed using Gas consumed by the operation and Gas price at the time of execution.

Gas consumption is the amount of computational and storage resources required to execute the transaction or a smart contract function. It depends on the complexity of the operation to be performed, these costs are determined by Ethereum Virtual Machine (EVM). Gas price is the cost we are willing to pay per unit of gas consumed. It defines the fees we are willing to pay for the miners to perform the transaction. Transactions offering higher gas price are executed faster and include them in the block. Gas price varies significantly depending on the network congestion.Let "G" represents the gas consumption (in gas units), and "P" represents the gas price (in gwei per gas unit). Total price "C" can be computed as described in the documentation [13] is computed as:

$$C = G * P$$

7.4.2 Transaction Time

Ethereum transaction time is the time required for transaction to be added in to the block and safely said to be confirmed. Transaction times is significantly influenced many factors. For simplicity, it can be considered transaction time depends on the confirmation time which in

turn relies on the block time and the number of confirmations required for transaction to be confirmed.

Let Block Time (T_B) is the time in ethereum which represents the average time it takes to mine a new block in the blockchain. It is approximately maintained at 15 seconds, but vary depending on the network congestion. Number of confirmation (N) is the number of confirmation a transaction needs before it is considered final. Transaction time "T" as described in [13] can be computed as:

$$T = T_B * N$$

7.5 Timing and Cost Analysis

Cost and timing analysis is performed on implemented PharmaChain 3.0 smart contracts which will help in estimating the cost of performing different functions in the smart contract along with revealing the potential vulnerabilities like out-of-gas errors and denial-of-service (DOS) attacks. To estimate the accurate gas costs and timings, smart contracts are deployed on Sepolia Testnet provided by Ethereum. These testnets are replicas of Mainnet with similar execution conditions. Hence, they provide more accurate insight into how designed DApp performs when deployed in Mainnet. Ethereum provides Goreli and Sepolia testnets, Sepolia was chosen for evaluating implemented PharmaChain 3.0 because of the easy availability of the test Ether from faucets. Resultant gas and time costs are clearly shown in Table 5.

From the table, when the transaction fee offered is higher, the transaction will be confirmed faster. Among the given operations, significant cost is associated with the deployment of a supplychain contract, creating a new unit and lot which is around 0.01256 ETH, 0.003871 ETH, and 0.0036830 ETH respectively. With Ethereum price $1,745 as of the day of experiments, the estimated cost for these functions is $21.91, $6.75, and $6.43 respectively. These overhead costs make the system not cost-effective in real-time but usage of private blockchain with nodes deployed and managed by the participating entities in the supply chain can eliminate these overhead costs and also process the transactions much faster than public blockchain.

8 Limitations and Challenges

Proposed PharmaChain 3.0 even though solves some of the drawbacks of current PSC. There are few limitation and challenges for implementing in real-world which are discussed below:

- Blockchain Scalability: Blockchain networks, especially public blockchains often have scalability issues. As more and more units/lots are tracked using public blockchain, the networks capacity can become a limitation which can result in higher transaction processing times and increased costs. As discussed previously, utilizing a private blockchain can address the issue to certain extent.
- Adoption: As pharmaceutical industry is highly regulated, resistance to change and lack of understanding can hinder the adoption of new technologies.
- Human Error and Bugs: Due to limited tools available for analyzing smart contracts, they are prone for human errors and vulnerabilities. These human errors and bugs in the smart contract can lead to unintended consequences and costly errors.
- External Data Feeds: Smart contracts cannot directly interact with the external data sources. Hence, oracles are used for managing external data feeds. Ensuring reliability and accuracy of these oracle data feeds is challenging.
- User Experience: Interacting with blockchain-based system is not as user-friendly as traditional systems. It includes wallets and multiple interfaces, needs to be carefully designed for widespread adoption.

9 Conclusion and Future Research

The proposed PharmaChain 3.0 presents blockchain leveraged novel solution for the counterfeit drug problem in PSC. It makes use of a decentralized blockchain system with a shared distributed ledger creating a transparent PSC. This avoids the centralized ERP systems thereby removing blind parties and enhancing the smooth operations and efficient communication in distributed entities. PharmaChain 3.0 also increases the accountability of the entities participating in the supply chain thereby ensuring that malicious entities are identified and punished easily to avoid false information propagation in the PSC.

It also provides a novel product serialization mechanism that makes use of unit and lot contract addresses to be used as unique identities GTIN and SSCC respectively. This proposed serialization mechanism can help in reducing the cost of operations along with providing improvised easier integration and adaptation of serialization systems. A robust Role-Based Access Control (RBAC) Mechanism is also implemented using smart contracts which help in managing the entities and adhering to regulatory compliance. PharmaChain 3.0 also utilizes off-chain storage for storing drug information like PIL which will be made available for the patients. Using this off-chain storage significantly reduced the

amount of information to be stored on-chain thereby reducing the cost of transacting on blockchain.

A proof-of-concept is implemented and functional, security, and cost analyses are performed to analyze PharmaChain 3.0 adaptability in a real-world scenario of PSC. Results from the analysis have shown the implemented PharmaChain 3.0 captures the functionality of PSC and follows DSCSA and PDMA regulations. Cost analysis has shown the cost overhead for performing transactions of creating units and lots, but this can be easily avoided by leveraging a private blockchain in which the nodes are deployed and managed by the supply chain entities instead of relying on the public blockchain. Security analysis has shown PharmaChain 3.0 system is robust against many of the most common security threats thereby making it a reliable and adaptable system to provide a safe PSC.

The current work can be further extended by including the backflow or reverse logistics which track and trace the returned drugs for various reasons like recalls, expired or damaged, excess inventory, etc. Along with that blockchain can also facilitate the funds processing between these distributed entities, hence a complete tradable supply chain can be built by including the financial flows. A complete tradable pharmaceutical supply chain combined with blockchain-based prescription systems can help in better-managing healthcare by providing the right medicine in the right location at the right time in the right quantities to the right patient.

Compliance with Ethical Standards

The authors declare that they have no conflict of interest and there was no human or animal testing or participation involved in this research. All data were obtained from public domain sources.

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References

1. Ahmadi, V., Benjelloun, S., Kik, M.E., Sharma, T., Chi, H., Zhou, W.: Drug governance: IoT-based blockchain implementation in the pharmaceutical supply chain. In: Proc. Sixth International Conference on Mobile And Secure Services (MobiSecServ). IEEE (2020). DOI 10.1109/mobisecserv48690.2020.9042950
2. Alkhoori, O., Hassan, A., Almansoori, O., Debe, M., Salah, K., Jayaraman, R., Arshad, J., Rehman, M.H.U.: Design and implementation of CryptoCargo: A blockchain-powered smart shipping container for vaccine distribution. IEEE Access **9**, 53786–53803 (2021). DOI 10.1109/access.2021.3070911
3. Alzahrani, N., Bulusu, N.: Securing pharmaceutical and high-value products against tag reapplication attacks using NFC tags. In: Proc. IEEE International Conference on Smart Computing (SMARTCOMP). IEEE (2016). DOI 10.1109/smartcomp.2016.7501715
4. Bapatla, A.K., Mohanty, S.P., Kougianos, E.: sFarm: A distributed ledger based remote crop monitoring system for smart farming. In: Internet of Things. Technology and Applications, pp. 13–31. Springer International Publishing (2022). DOI 10.1007/978-3-030-96466-5_2
5. Bapatla, A.K., Mohanty, S.P., Kougianos, E., Puthal, D.: PharmaChain 2.0: A blockchain framework for secure remote monitoring of drug environmental parameters in pharmaceutical cold supply chain. In: Proc. IEEE International Symposium on Smart Electronic Systems (iSES) (2022). DOI 10.1109/ises54909.2022.00046
6. Bapatla, A.K., Mohanty, S.P., Kougianos, E., Puthal, D.: PharmaChain 3.0: Blockchain integrated efficient QR code mechanism for pharmaceutical supply chain. In: Proc. OITS International Conference on Information Technology (OCIT). IEEE (2022). DOI 10.1109/ocit56763.2022.00121
7. Bapatla, A.K., Mohanty, S.P., Kougianos, E., Puthal, D., Bapatla, A.: PharmaChain: A blockchain to ensure counterfeit-free pharmaceutical supply chain. IET Networks **12**(2), 53–76 (2022). DOI 10.1049/ntw2.12041
8. Bapatla, A.K., Puthal, D., Mohanty, S.P., Yanambaka, V.P., Kougianos, E.: EasyChain: an IoT-friendly blockchain for robust and energy-efficient authentication. Frontiers in Blockchain **6** (2023). DOI 10.3389/fbloc.2023.1194883
9. Blackstone, E.A., Fuhr, J.P., Pociask, S.: The health and economic effects of counterfeit drugs. American health and drug benefits **7**, 216–224 (2014)
10. Bocek, T., Rodrigues, B.B., Strasser, T., Stiller, B.: Blockchains everywhere - a use-case of blockchains in the pharma supply-chain. In: Proc. IFIP/IEEE Symposium on Integrated Network and Service Management (IM), pp. 772–777 (2017). DOI 10.23919/inm.2017.7987376
11. Cai, Y., Li, X.W., Chen, H., Liu, J.R.: Prototype implementation of traditional chinese medicine quality traceability system based on two-dimensional barcode. In: Proc. 10th International Conference on Information Technology in Medicine and Education (ITME). IEEE (2019). DOI 10.1109/itme.2019.00044
12. Debe, M., Salah, K., Jayaraman, R., Arshad, J.: Blockchain-based verifiable tracking of resellable returned drugs. IEEE Access **8**, 205848–205862 (2020). DOI 10.1109/access.2020.3037363
13. Ethereum: Ethereum development documentation. URL https://ethereum.org/en/developers/docs. Last Accessed: 2023-10-23
14. Food, of Criminal Investigations, D.A.O.: New england compounding center pharmacist sentenced for role in nationwide fungal meningitis outbreak. URL https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/press-releases/january-31-2018-new-england-compounding-center-pharmacist-sentenced-role-nationwide-fungal. Last Accessed: 2023-05-06

15. Food, U., Administration, D.: Drug master files (dmfs). URL https://www.fda.gov/drugs/forms-submission-requirements/drug-master-files-dmfs. Last Accessed: 2023-05-06
16. Food, U., Administration, D.: New drug application (nda). URL https://www.fda.gov/drugs/types-applications/new-drug-application-nda. Last Accessed: 2023-05-06
17. Humayun, M., Jhanjhi, N., Hamid, B., Ahmed, G.: Emerging smart logistics and transportation using IoT and blockchain. IEEE Internet of Things Magazine **3**(2), 58–62 (2020). DOI 10.1109/iotm.0001.1900097
18. Institute, P.S.: Incident trends. URL https://www.psi-inc.org/incident-trends. Last Accessed: 2023-05-06
19. Kaufmann, L., Thiel, C., Becker, A.: Supply chain management in the mexican pharmaceutical industry. 16th annual North American research/teaching symposium on purchasing and supply chain management (2005)
20. King, B., Zhang, X.: Securing the pharmaceutical supply chain using RFID. In: Proc. International Conference on Multimedia and Ubiquitous Engineering (MUE'07). IEEE (2007). DOI 10.1109/mue.2007.186
21. Musamih, A., Salah, K., Jayaraman, R., Arshad, J., Debe, M., Al-Hammadi, Y., Ellahham, S.: A blockchain-based approach for drug traceability in healthcare supply chain. IEEE Access **9**, 9728–9743 (2021). DOI 10.1109/access.2021.3049920
22. Nakamoto, S.: Bitcoin: A peer-to-peer electronic cash system. URL https://bitcoin.org/bitcoin.pdf. Last Accessed: 2023-05-06
23. Onieva, E., Osaba, E., Angulo, I., Moreno, A., Bahillo, A., Perallos, A.: Improvement of drug delivery routes through the adoption of multi-operator evolutionary algorithms and intelligent vans capable of reporting real-time incidents. IEEE Transactions on Automation Science and Engineering **14**(2), 1009–1019 (2017). DOI 10.1109/tase.2015.2476508
24. Organization, W.H.: Substandard and falsified medical products. URL https://www.who.int/en/news-room/fact-sheets/detail/substandard-and-falsified-medical-products. Last Accessed: 2023-05-06
25. (PDSA), P.D.S.A.: 2023 dscsa requirements. URL https://pdsaonline.org/dscsa-information/phase-ii-implementation/. Last Accessed: 2023-05-06
26. Qiu, J., Liang, X., Shetty, S., Bowden, D.: Towards secure and smart healthcare in smart cities using blockchain. In: Proc. IEEE International Smart Cities Conference (ISC2). IEEE (2018). DOI 10.1109/isc2.2018.8656914
27. Rahman, M.S., Yoshida, N., Tsuboi, H., Tomizu, N., Endo, J., Miyu, O., Akimoto, Y., Kimura, K.: The health consequences of falsified medicines- a study of the published literature. Tropical medicine and international health : TM and IH **23**, 1294–1303 (2018). DOI 10.1111/tmi.13161
28. Renschler, J.P., Walters, K.M., Newton, P.N., Laxminarayan, R.: Estimated under-five deaths associated with poor-quality antimalarials in sub-saharan africa. The American journal of tropical medicine and hygiene **92**, 119–126 (2015). DOI 10.4269/ajtmh.14-0725
29. Saeed, M.Q., Bilal, Z., Walter, C.D.: An NFC based consumer-level counterfeit detection framework. In: Proc. Eleventh Annual Conference on Privacy, Security and Trust. IEEE (2013). DOI 10.1109/pst.2013.6596047
30. Saindane, P., Jethani, Y., Mahtani, P., Rohra, C., Lund, P.: Blockchain: A solution for improved traceability with reduced counterfeits in supply chain of drugs. In: Proc. International Conference on Electrotechnical Complexes and Systems (ICOECS) (2020). DOI 10.1109/icoecs50468.2020.9278412
31. Schapranow, M.P., Müller, J., Zeier, A., Plattner, H.: Costs of authentic pharmaceuticals: research on qualitative and quantitative aspects of enabling anti-counterfeiting in RFID-aided supply chains. Personal and Ubiquitous Computing **16**(3), 271–289 (2011). DOI 10.1007/s00779-011-0390-4
32. Shaik, C.: Preventing counterfeit products using cryptography, QR code and webservice. Computer Science and Engineering: An International Journal **11**(1), 1–11 (2021). DOI 10.5121/cseij.2021.11101
33. Standards, G.: Gs1 standards in healthcare. URL https://www.gs1.org/industries/healthcare/standards. Last Accessed: 2023-05-06
34. Subramanian, G., SreekantanThampy, A., Ugwuoke, N.V., Ramnani, B.: Crypto pharmacy – digital medicine: A mobile application integrated with hybrid blockchain to tackle the issues in pharma supply chain. IEEE Open Journal of the Computer Society **2**, 26–37 (2021). DOI 10.1109/ojcs.2021.3049330
35. tracelink: How much will serialization really cost? URL https://t.ly/YVooQ. Last Accessed: 2023-10-23
36. US, G.: Get authentic u.p.c. barcodes from gs1 us. URL https://t.ly/CDgk0. Last Accessed: 2023-10-23
37. Yousefi, N., Alibabaei, A.: Information flow in the pharmaceutical supply chain. Iranian journal of pharmaceutical research : IJPR **14**, 1299–1303 (2015)