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Review

Blockchain-enabled pharmaceutical cold chain: Applications, key challenges, and future trends

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ABSTRACT

Cold chains are temperature-controlled supply chains and have a high priority from the managerial point of view. The pharmaceutical cold chain, in particular, is a complex and sensitive chain that needs to be managed effectively based on its direct effects on public health and peoples' life. Blockchain technology as an emerging distributed solution has been attracting proliferating studies over recent years. The main objective of this paper is to address how blockchain would meet the requirements of a pharmaceutical cold chain such as pharmaceutical digital identity, serialization and traceability, data integrity, transparency, and waste management. Besides, we reviewed the current limitations of the blockchain-enabled pharmaceutical chain to provide deep insights into the existing research challenges and clarify future study directions. Moreover, different case studies of blockchain-based pharmaceutical and medicine projects that deal with these challenges for diverse purposes are discussed. This study represents the various solutions by which blockchain technology would help attain the pharmaceutical cold chain objectives.

Contents

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1. Introduction

The demand for products like fruits, flowers, seafood, etc. depends on their freshness. Hence, to maintain the freshness, these products are constantly stored in an artificial (mostly cold) controlled environment (Gupta et al., 2019). Supply chain management requires special attention to such products with limited durability, as well as items that require special equipment and facilities for sale, storage, and distribution. This led to the appearance of Cold Chain Management (CCM) (Shih and Wang 2016). Products such as pharmaceutical products, chilled food, frozen foods, and short-lived products are sensitive to temperature, humidity, and lighting intensity need a cold supply chain to manage environmental changes. Environmental changes and fluctuations reduce the quality of products and thus have negative effects on consumer health (Tsang et al., 2018). This issue makes more risks when the product is pharmaceutical. Many medicines need to preserve in a certain range of temperatures to remain effective. The ability to investigate the temperature conditions and validity of medicines permit medical professionals or patients to discard drugs that are inactive or ineffective. When suitable medication is recognized, the supply chain of that medication will require to be monitored closely for the validity of medication and the useful ingredients are temperature sensitive (Dwivedi et al., 2019). Information and communication technology (ICT) systems are used to control the fluctuations of environmental conditions (Monteleone et al., 2017).

These technologies help managers to build various models of supply chain systems using a data-driven approach (Madhwal and Panfilov 2017). Considerable developments occurred in the temperature monitoring with the Internet of Things (IoT), radio-frequency identification (RFID) tags, sensors, barcodes, GPS tags and chips and by using them, the location of products, packages, and shipping containers are traceable during the time (Monteleone et al., 2017; Kshetri 2018).

There are some problems in utilizing IoT devices about their vulnerability against hacking and manipulation. Hence, using a decentralized, autonomous, and trusted network such as blockchain is considered to be necessary (Kshetri 2018). Blockchain can be applied to reduce the vulnerability of devices and thus make them more secure (Jochumsen and Chaudhuri 2018). It is also effective in integrating information and increasing the coordination of chain members. In the last decades, there has been a growing interest in blockchain applications in a variety of scopes. In fact, blockchain technology is a peer-to-peer network to record and store information in a safe, integrated, and accessible manner by using impenetrable encryption techniques. Blockchain technology enables involved parties in the supply chain to have more privacy preservation, data transparency, and tamper-proof system throughout the supply chain (Min 2019). Furthermore, it would improve the problem of trace and track the temperature of products in cold chains by the adoption of smart contracts integrated by IoT devices (Bocek et al., 2017).

As mentioned, blockchain is applicable in pharmaceutical cold chain automation and management. The total expected advantages of utilization of blockchain in pharmaceutical cold chains are determining what actions are in progress and performing by who, when, and where (Kshetri 2018). It creates trust among the pharmaceutical cold chain members by presenting them the permissions to know about the product's quality status at any moment and therefore increases the efficiency and decreases the costs (Koetsier 2017). Applications of blockchain in pharmaceutical data integration prevent resources to be wasted by tracing the temperature of products consequently at any step of the logistic process, protect information from being stolen or changed, and creates a competitive advantage. Mainly, blockchain brings noticeable benefits such as serialization, tracing, securing IoT devices, smart contracts, avoiding counterfeiting, and tamper-proof information sharing systems (Jochumsen and Chaudhuri 2018). In the following the main contributions of this study are mentioned:

— A wide range of blockchain applications in the pharmaceutical domain such as digital identity, serialization and traceability, data integrity, transparency, and waste management are considered.
— A deep insight into the existing research challenges is presented, and future directions in the blockchain-based pharmaceutical cold chain are discussed.
— Different case studies of blockchain-based solutions in pharmaceutical and medicine projects are presented.

The remainder of this paper is organized as follows. Section 2 provides the main necessary background knowledge cold supply chain, and the possible application domains. In Section 3, we comprehensively review applications of blockchain in the pharmaceutical chain including serialization and traceability, data integrity, transparency, and waste management. The different cases studied and imperial solutions of blockchain in medicine projects are discussed in Section 4. The discussion and the possible challenges are discussed in Section 5. Finally, the conclusion is presented in Section 6.

2. Background

2.1. Cold chain

A cold chain is a temperature-controlled supply chain. A cold chain is a type of supply chain with controlled temperature from the stage of production, through to the transportation stages, storage, distribution processes, and delivery to the end-user. Briefly, a cold chain is a temperature-controlled supply chain of sensitive goods. The cold chain makes modern life possible through the safe transportation of food, pharmaceuticals, and other environmentally sensitive products (ESPs) from the moment they are grown or extracted, during the manufacturing process, and to the final consumers. Based on the type of the product, their transportation is accomplished by refrigerated railcars, trucks, cargo ships, and air cargo (Rodrigue and Notteboom 2014). Cold chains play a vital role in global trade. While there are millions of people starving or suffering from diseases in the world, a poor cold chain makes billions of fresh foods and medicines waste.

Cold chains require evaluation and control systems based on the characteristics of the products to keep their freshness and quality during the process to get to consumers. Therefore, it is necessary to monitor the temperature in the whole cold chain process to maintain the constant temperature and guarantee the quality and safety of products in the cold chain (Xiao et al., 2019). For the successful implementation of a cold chain, we should know the type and characteristic of the product. Based on studies that have been conducted in the cold chain domain, we classify them into four categories including perishable foods such as dairy products and beverages, flowers and ornamental plants, fresh agricultural products, and pharmaceutical products as presented in Fig. 1.

2.1.1. Perishable products

A cold chain is an essential part of the food products supply chain and more especially when the products are perishable. Perishable foods like cooked, ready to eat, and high-risk foods should keep refrigerated or frozen to preserve until consumption. This category includes some fresh foods such as raw vegetables, raw fruits, raw milk, dairy products, fish, poultry, red meats, and ready-to-eat sandwiches. In the cold chains of food and perishable products, there are higher risks of food waste, increases costs, and often health risks, which have a significant societal cost, if spoiled goods end up on the market. Perishable foods need correct humidity and ventilation control in cold storage. These products are hygroscopic materials while their properties vary significantly with the humidity of the air around them, not just with temperature. Hence, they need a smart cold chain to make efficient and timely management against the problems through the chain from "farm to fork" (Tsai and Pawar 2018). Inefficiencies in food cold chain management may lead to post-harvest food which is a considerable issue in populated countries (Cerchione et al., 2018). This inefficiency will also happen when the requirements of the food cold chain, especially the specific nature of temperature-sensitive perishable products are not provided (Bremer 2018).

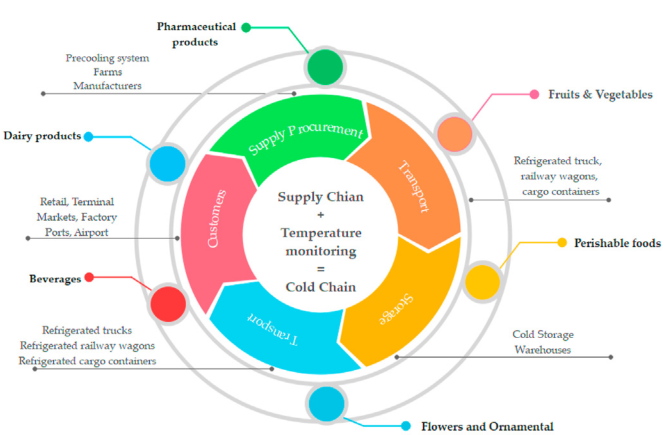

Fig. 1. Cold chain products categories.

Supply chain management is always in a challenge with controlling the risks of conditional changes that lead to reduce product quality and consumer health too. Temperature is the main issue in the quality of the perishable product that affects the shelf life of products. In addition to temperature, other conditions such as humidity and lighting intensity are necessary to be monitored to ensure the products are handled in desired conditions and prevented from quality loss. Although frozen storage consumes high-energy for the preservation of food products, cool storage involves the problem of bacterial growth. Therefore, technology-based monitoring systems must monitor these sensitive data and control the conditions of the products in all stages of the cold chain continuously (Çeken and Abdurahman 2019). Filling the gap in information flow is necessary for decentralized cold chain systems (Tian 2017). Such systems provide benefits more than traceability such as shelf-life prediction, sales premium, precision agriculture, and reduction of assurance cost throughout the food cold chain (Pang et al., 2015).

It should be noted that the environmental pollution of the cold chain is a controversial issue. It consumes lots of energy and spreads high levels of greenhouse gases. Cold chains need refrigerated warehouses and trucks to store and transport the products at low temperatures or under the freezing point. These facilities consume lots of energy for the refrigeration process and therefore, make higher carbon dioxide emissions in power generation facilities. Increased knowledge of companies about global warming impact, made environmental considerations be taken into account in cold chain drawbacks (Saif and Elhedhli 2016). The other key obstacles to CCM efficiency include lack of expertise, lack of national-level quality and safety-control measures, supply chain density, deficient infrastructure and information systems, costly installation and operation of cold chains, deficiencies in training and standardization, lack of government support, and social norms (Gligor et al., 2019).

2.1.2. Flowers and ornamental plants

Cold chain management of cut flowers and ornamental plants is important because of the long distances between greenhouses to their markets. Cold chain logistics of flowers and ornamental plants, contains three stages; from the suppliers (growers) to the wholesalers, to the retailers, and finally to the customers (Babalola et al., 2011). Changes in environmental conditions are the main challenge that these kinds of cold chains may constantly face. Flowers based on their types require a pre-defined storage temperature and a maximum period of storage so that their quality and vase life remains safe. In these cases, well monitoring of the cold chain ensures a longer vase life and even higher prices for products. Slight damage to the flowers can bring loss of income for the stakeholders (Macheka and Kockelkoren 2012).

On-farm postharvest management contains hydration and vase life parameters. For postharvest management, temperature, physical damage, and hydration were the main issues during storage and transportation. Product temperature varies in each step of the chain, especially during loading (Bogataj et al., 2005). At the postharvest phase, any point of the chain where flowers are not under cold storage, from their harvest to their loading into the plane, is a weak link (Singh et al., 2002; Çelikel et al., 2010). Therefore, suppliers should make sure that no break occurs in the process.

Maintaining conditions, especially during transportation, may cause quality problems (Hosseini and Hajishams 2012). Damaged flowers, bent stems, uneven opening, and parasites result from adverse conditions and the temperature is usually the most important factor between them. Logistics conditions such as the air quality, the temperature, the humidity, the room pressure, and even the lighting level are the main postharvest problems of flower cold chains. For instance, the lighting parameter directly affects the quality of the fresh flowers, but the bacterial growth should be under the control with suitable temperature and humidity (Smith 2006). Moreover, the dose of oxygen and carbon in the chain environment can also affect the quality of these products, given that flowers continue to breathe after being cut. It needs to be noted that sanitation is an important factor. In fact, everything such as buckets, cutters, coolers, benches should be cleaned with an approved disinfectant cleaner. As studies show that dirty buckets can reduce the vase life of a flower by up to 20% (florint, 2020).

The availability of a temperature-controlled room is important for the quality of cut flowers and it would begin right from the farm, to the refrigerated trucks that transport flowers to the warehouses, to the airport and airplane in-country, till it reaches the final destination. Transporting vehicles of these cold chains also play an important role. Refrigerated distribution vehicles are necessary for cold chain logistics. Notably, all personnel handling life products have enough knowledge to ensure there is no failure in any of the stages. Technology-based monitoring systems like Time-Temperature Indicators (TTI), Radio frequency identification (RFID), etc. can play an effective role in tracing the conditions and location of the products in order not to lose quality.

2.1.3. Fresh agricultural products

Following the previous two groups, agriculture supply chain management (ASCM) faces lots of challenges like environmental conditions, many actors involved, and lack of skilled workforce. Therefore, applying information and communications technologies (ICT) in ASCM is useful. These technologies in ASCM are used to reduce wastage and improve productivity and sustainability throughout the chain (Luthra et al., 2018). Freshness is the most important subject in fresh agricultural cold chains. To manage this, many researchers focused on the importance of the last mile, including the final delivery of products to customers, which is one of the most expensive, and polluting sections of the logistics chain (Hsiao et al., 2018). While customers announced a multi-temperature joint distribution system is a constant problem (Chen et al., 2018). Products as tree fruit, berries, melons, vegetables, fresh herbs, mushrooms, and sprouts belong to this type of cold chain must always maintain in a controlled environment because their freshness affects their demands at the sales stage. These kinds of products also go a long distance from produce to sale and pass through many stages of transportation. In this sense, refrigerated vehicles are key factors in agricultural cold chain logistics (Gupta et al., 2019).

Chain connections and channel management should be considered in the cold chain for their impact on pricing decisions and profits (Yu and Xiao 2017). Several sensors that measure items such as biological status, integrity, time-temperature, and humidity would be used with the help of technology-based systems to evaluate the decrement and deterioration of fresh products (Cai et al., 2013; Bibi et al., 2017). Some factors have an important influence on the technology adoption of monitoring systems in the agriculture cold chain. Technical factors are complexity, compatibility, perceived benefit, and cost. The scale of the enterprise, executive support, trust among the businesses in the supply chain, and technical knowledge are related to the organizational factors. Also, external pressure and government support are in the category of environmental factors (Lin et al., 2016).

2.1.4. Pharmaceutical industry

The supply chain of medicines includes the pharmaceutical cold chain as well as the healthcare supply chain, associated with pharmaceutical companies, hospitals, health centers, and pharmacies. Pharmaceuticals products are usually transported in cold packages which are arranged in pallets onboard aircraft. While flowers and other agricultural packages in cardboard boxes are arranged in layers in properly ventilated pallets onboard aircraft (Babalola et al., 2011).

Pharmaceuticals manufacturers must comply with the related standards prescribed by FDA named cGMP (current Good Manufacturing Practices) and the logistics of the company must comply with standards called GDP (Good Distribution Practices) (Bishara 2006). This is because pharmaceutical products that are not well-produced, stored, or transported can cause major problems for patients when consumed. As discussed, the most important challenge of pharmaceutical and healthcare cold chains is temperature control should be kept the desired quality of the product to reach the final consumer (Bogataj et al., 2005; Kapoor et al., 2018). With a high impact on patients and consumer safety, it is one of the main factors of immunization in many countries (Brison and LeTallec 2017) and is not only limited to developing countries (Duijzer et al., 2018). For instance, some kinds of vaccines, like varicella-containing vaccines, require refrigeration and freezing equipment in transportation (Goldberg and Karhi 2019). While reports stated non-standard temperature ranges in 35.3% of shipment and 21.9% of refrigerators for vaccines (Matthias et al., 2007).

Each step in the cold chain depends on the previous one and affects the next. A defect in chain connections leads to quality loss and additional costs (Chen and Shaw 2011). Therefore, risk identification is necessary which depends on product amount, quality, and disruption times throughout the chain. Equipment failure, unreliable electricity power systems, undesirable road conditions in many developing countries could be examples of infrastructure risks that cause breakdowns in the pharmaceutical cold chain (Lauton et al., 2019). Inadequate training of involved personnel is a human risk that affected the quality of the pharmaceutical cold chain (Hibbs et al., 2018). The perturbation challenge in the pharmaceutical cold chain comes from its complex nature and involving many members with diverse strategies (Rossetti et al., 2011) or whose tasks do not follow a determined standard format on the other side (Boyer and Pronovost 2010). On the other hand, products' return is another issue that makes the cold chains of the pharmaceutical products different from the others. It reduces the company profits and destroys its reputation. To handle this, accurate tracking and data clarity, standard requirements, suitable storage, and an anti-counterfeit system must be provided to specify the defective products (Kabir 2013).

Here, techniques including IoT in which the radio-frequency identification (RFID), wireless sensor networks (WSN), and middleware and cloud computing are employed, have been used in the pharmaceutical industry, too (Zhong et al., 2017; Ben-Daya et al., 2019). These technologies improve the coordination and communication in the pharmaceutical cold chain by making the information flow between manufacturing, logistics, sales, and consumption processes able to be shared and monitored in real-time. As a result, the whole chain can be effectively controlled by managers (Ding 2018) by connecting multiple systems to the same platform (Urbano et al., 2020). For instance, IoT can especially be used in real-time temperature monitoring in the pharmaceutical and healthcare industries (Monteleone et al., 2017). It brings the capability of being up to date with current regulations, reducing the costs of wastes through transfers, and on-time location of products at any stage (Balachandar and Chinnaiyan 2020). On the other hand, the technology of temperature monitoring can be embedded with passive RFID and WSNs, which are available solutions to gather real-time sensor data without the need for any external powering (Zhou and Chakrabartty 2017). These technologies monitor data such as item identity and environmental factors. Based on the product characteristics, there are some environmental factors needed to be controlled as summarized in Table 1. For instance, some types of sensors such as TTI, indicator sensors, and contamination sensors are used to monitor the product in all stages of cold chain production for processing, distribution, and consumption (Pal and Kant 2020). However, such monitoring applications will create a large volume of data in the corporate information technology system, which is difficult to manage and may incur the cost of purchasing and licensing the local database.

In order to overcome the aforementioned challenges, integration of cold chain with blockchain technology would bring innovative at the same time practical solutions. Blockchain can settle the problems of counterfeit medicines and medical products by giving a unique code to each product (Radanović and Likić 2018). Moreover, blockchain technology can improve Electronic Health or Medical Records (EHR/EMRs) and deal with its difficulties such as cost, fragmentation of patient data, privacy issues, stealing and misusing patients' information, and fraud (Shuaib et al., 2019), that in the following sections we will discuss in details. Here, we classified and summarized the literature based on cold chain categories, year of publication, their methodology, and application scenario as presented in Table 2.

2.2. Blockchain

Blockchain is a cutting-edge technology with various applications such as cryptocurrency, financial services, risk management, public and social services. Bitcoin is the most popular application of blockchain as cryptocurrency (Zheng et al., 2018). Other applications of this technology have also received attention from different industrial sectors such as food (Olsen et al., 2019) and pharma (Clark and Burstall 2018).

Blockchain can be defined as a public ledger in which all data and transactions are recorded in a chain of blocks. Three main parts of each block are data, hash block, and the previous hash block. When a transaction is recorded in a block, a cryptographic hash function encodes the contents of this transaction to an alphanumeric string of fixed length and makes transaction hash values. Each block includes the hash value of the previous block. Hence, all blocks are joined to each other through their hashes. Therefore, if someone wants to change the data of a block, its hash value changes, and all the following blocks must be refined (Bamakan et al., 2020). Fig. 2, shows the blockchain structure with three blocks.

As presented in Fig. 2, each block consists of the block header and the block body. The block header is made with six sections: version number, the block hash, the hash of the previous block, the timestamp, the nonce, the Merkle root, and the block body consists of transactions (Zheng et al., 2018). Several transactions can be accumulated in one block. Transactions are registered in each block through a hash function and each transaction takes a hash. The final hash value of a block (Merkle root) is generated by the Merkel tree function. A hash tree, or the Merkle tree stores hashes of transactions in an upside-down binary tree. The lowest level of the tree (called the leaf-level) and the hash values of transactions store at it. The hash of the hashes of two corresponding leave nodes reserve at level one above the leaf-level of the tree. Finally, the last transaction hash stores in the root of the tree that is called the Merkle root. Using the Merkle tree and Merkle root mechanism remarkably reduces the levels of hashing to be computed and provides faster verification and lower cost of data transmission (Bamakan et al., 2020).

2.2.1. Public, private, and consortium blockchain

Three categories of blockchain according to the type of access for their users are public, private, and consortium (Perera et al., 2020).

— Public blockchain technologies permit anyone to take participate in another transacting party. It does not mean little to no privacy for transactions because public blockchain uses consensus algorithms such as proof of work (PoW) and proof of stake (PoS), etc. to make the chain safe. Bitcoin and Ethereum can be considered as examples of the public blockchain.

— The private blockchains allow authorized participants to link to the network. In a permissioned blockchain, contributors can be restricted to those who are pre-approved. Moreover, different access levels of information in the ledger can be provided for participants. Private blockchain prepares high privacy and safety mechanisms. A consortium blockchain is partly similar to a private blockchain solution without a single owner constitution and is usually known as federated blockchains. The consensus mechanism in private blockchains is defined by a single central authority. Here, Practical Byzantine Fault Tolerance (PBFT) and Delegated Byzantine Fault Tolerance algorithm are the most common consensus techniques are applied in permissioned blockchain. It needs

Table 1
The main indicators to monitor in the cold chain.

Environmental Factor	Perishable products	Flowers and ornamental Plants	Fresh agricultural products	Pharmaceutical products
Temperature	✓	✓	✓	✓
Sanitation	✓		✓	✓
Humidity	✓	✓	✓	✓
Lighting		✓		✓
Ventilation	✓	✓	✓	✓
Segregation	✓	✓	✓	✓
Atmosphere		✓		✓
Oxygen		✓		
Carbon		✓		

Table 2
Literature review summary and classification.

No.	Sub-Category	Year	Authors	Methodology	Application Senario
1	**Perishable products**	2018	Tsai and Pawar	ICT applications	Cold Chain logistics
2		2018	Cerchione, Singh et al.	Literature review	Cold Chain Management
3		2018	Bremer	Object-oriented modeling approach	Cold Chain logistics
4		2019	Çeken and Abdurahman	Regression technique	Cold Chain Temperature Monitoring
5		2017	Tian	HACCP method	Cold Chain logistics
6		2015	Pang, Chen et al.	Internet-of-Things (IoT) application	Food supply chain Value-centric design
7		2016	Saif and Elhedhli	Mixed-integer Programming	Cold Chain design
8		2019	Gligor, Gligor et al.	Literature review	Supply Chain agility and resilience
9	**Flowers and ornamental plants**	2011	Babalola, Sundarakani et al.	Literature review	Cold Chain practices in the floral industry
10		2012	Macheka and Kockelkoren	Literature review	Realizing the added value of investing in cut flower cold chains
11		2010	Çelikel, Cevallos et al.	Internet-of-Things (IoT) application	Cold Chain logistics
12		2012	Hosseini and Hajishams	Literature review	Cold Chain logistics
13	**Fresh agricultural products**	2018	Luthra, Mangla et al.	Internet of Things (IoT) application	Agriculture Supply Chain Management
14		2018	Hsiao, Chen et al.	Genetic Algorithm (GA)	Cold Chain logistics
15		2018	Chen, Lu et al.	Integer programming	Cold Chain logistics
16		2019	Gupta, Chaudhuri et al.	Internet of Things (IoT) application	Third-Party Logistics (3 PL) provider
17		2017	Yu and Xiao	Stackelberg game	Pricing Decision
18		2013	Cai, Chen et al.	Incentive scheme applications to coordinate supply chain	Supply Chain coordination
19		2017	Bibi, Guillaume et al.	RFID sensor application	Food quality monitoring
20		2016	Lin, Lee et al.	Literature review	IoT technology adoption in cold chain
21	**Pharmaceutical industry**	2006	Bishara	Literature review	Cold Chain management
22		2017	Brison and LeTallec	Literature review	Cold Chain Management
23		2018	Duijzer, van Jaarsveld et al.	Literature review	The Vaccine supply chain
24		2019	Goldberg and Karhi	Online Multi type Bin-Packing Model	Cold Chain logistics
25		2007	Matthias, Robertson et al.	Literature review	Vaccine cold chain temperature monitoring
26		2011	Chen and Shaw	Artificial Neural Network	Cold chain temperature monitoring
27		2019	Lauton, Rothkopf et al.	Mathematical modeling	Contract to buy essential medicines in low-income countries by Purchasing organizations (POs)
28		2018	Hibbs, Miller et al.	VAERS database review	vaccine cold chain management
29		2011	Rossetti, Handfield et al.	Multiple interviews	Pharmaceutical supply chain Management
30		2010	Boyer and Pronovost	Literature review	Costs and Quality of Medicine
31		2013	Kabir	Literature review	Reverse logistics
32		2017	Zhong, Xu et al.	Literature review	Intelligent Manufacturing
33		2019	Ben-Daya, Hassini et al.	Literature review	Internet of Things (IoT) applications
34		2018	Ding	Literature review	Sustainable Pharmaceutical Supply Chain
35		2020	Urbano, Perles et al.	RFID Tags and IoT application	Temperature Traceability System
36		2017	Monteleone, Sampaio et al.	Internet of Things (IoT) application	Medicine Cold Chain Temperature Monitoring
37		2020	Balachandar and Chinnaiyan	Internet of Things (IoT) application	Pharma Cold Chain Monitoring
38		2017	Zhou and Chakrabartty	Modeling of Self-Powered Temperature Sensor	Cold Chain Time-Temperature Monitoring
39		2020	Pal and Kant	Several sensing technologies applications	Cold Chain logistics
40		2018	Radanović and Likić	Blockchain applications	Data access control in medicine industry
41		2019	Shuaib, Saleous et al.	Blockchain applications	Challenges of Medicine information systems

to be mentioned that energy efficiency and high throughput are considered as their advantages compared to the proof of work and proof of stake algorithms.

— Consortium blockchains permit all users to view data, but some of them are allowed to write to the blocks. Consortium blockchain helps the trust, cooperation, and transparency partnering rise. Common examples of consortium blockchains are Corda R3, EWF, B3i, and Quorum (Perera et al., 2020).

Furthermore, there is a concept of open and closed blockchain beyond the public, private and consortium blockchain. Private and public blockchain relate to the user's access level for writing information from blockchain and open and closed blockchain relate to the user's access level for reading data from the blockchain. There can be practical applications based on public and open, public and closed, private and opened, and private and closed. Applications of these four kinds of approaches are shown in Fig. 3.

As shown in Fig. 3, the public and open approach can be applied in betting and currencies where openness is required. Moreover, the application of the public and closed approach can be in voting where anyone can write data in blockchain but no one can read data from it. Furthermore, the private and open blockchain approach can be used where the participants are not allowed to write, but they can read data such as the supply chain.

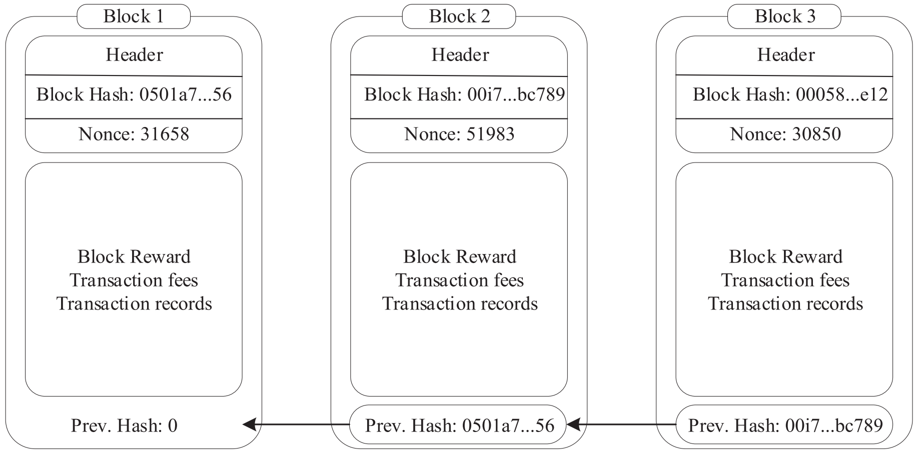

Fig. 2. Blockchain structure with three blocks.

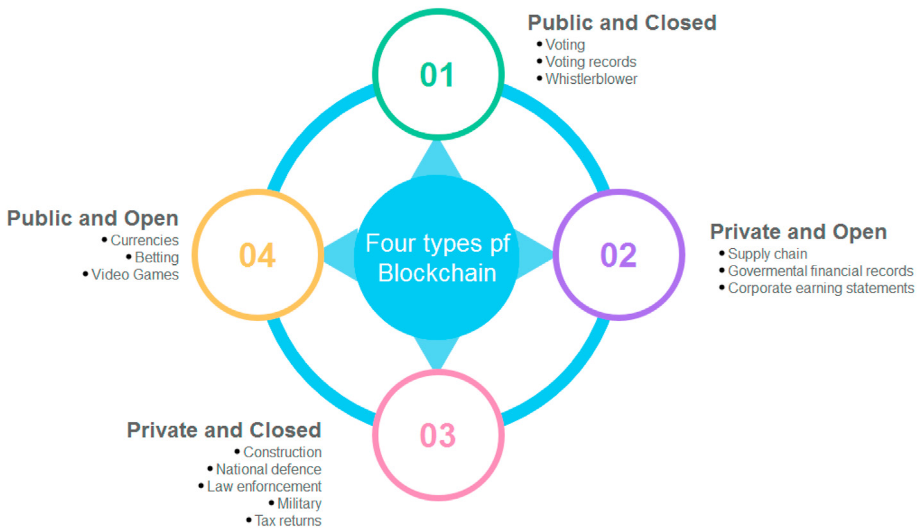

Fig. 3. Different types of blockchain-based on the user's access level.

2.2.2. *Trustless system*

One significant aspect of blockchain technology is a system of trust across different users. The trust system enables users to consensually and digitally agree to any change in the database (Hastig and Sodhi 2020). If end-users do not know the process of blockchain and it is vague for them, the distrust aspect of blockchain will be reduced substantially. The proprietary feature of closed blockchains makes them less accessible for some of their end-users. Therefore, closed blockchains limit trustlessness, although they would be more attractive for representing databases into existing ledger and registry applications in a maturity period of five to ten years. Interactions in the closed blockchain are based on legacy user authentication interfaces that cause vulnerability to the system while in open blockchains, transaction processing is inherently neutral and equidistant from all parties and uses trustlessness to the full extent. Open blockchains apply peer-to-peer networks among end-users in which helps them to know the process of blockchain. They are built to be resistant to malicious behavior and malfunctions. Bitcoin is one of the most famous open blockchain (Garzik 2015). It should be noted that a trustless system in closed blockchain can be useful when the provenance and authenticity of information are required to confirm such as the pharma supply chain (Nageswar and Yellampalli 2019).

2.2.3. *Smart contracts*

Smart contracts are computer programs running and storing across the blockchain network. Smart contracts should facilitate, verify, and enforce the process of a contract (Handoyo et al., 2018). Each smart contract has a contract hash and a contract address which is used for storing and securely resuming contracts (Soundarya et al., 2018). Identification of each smart contract is done through a specific address includes of script code, a currency balance, and storage space in the shape of a key/value store. Once the smart contract is created and executed no one can change the contract's code (Handoyo et al., 2018). Contract formation is one of the first steps for beginning supply chain activities. So, contractual conflict resulting from fraud, misunderstanding, and performance failures can disrupt supply chain activities. Forming a smart contract can be one of the possible ideas to solve these problems. These contracts not only determine the rules and penalties around a contractual agreement such as a traditional contract but also enforce those rules automatically. The Self-verifying and self-executing properties of a smart contract can improve the agreement, decrease risk, and increase efficiencies across the entities (Min 2019).

2.2.4. Zero-knowledge proof

Although transparency can be obtained in the pharmaceutical cold chain by blockchain technology (Surjandy et al., 2017), it arises other issues like privacy, i.e., information once joined to the blockchain is added forever and is used in the public scope, which permits third parties to monitor and predict patients' manner or habits. However, the privacy of the transactions is an essential part of healthcare situations when the prepared data is required to be permitted for monitoring and anticipating patients' manners or habits.

The zero-knowledge proof (ZKP) technique is one solution for raising privacy in the blockchain. The basic idea of the ZKP is that one participant (prover) persuades another participant (verifier) that its statements are true without disclosing the content of that statement. For example, a person who knows the secret gives the hash of a random number to convince the verifier that there exists a number with this hash value, without revealing its content. Therefore, ZKP can be used in blockchain to get a certain level of transparency while a transaction is maintained (Shukla and Agrawal 2020).

3. Applications of blockchain in pharmaceutical cold chain

Naturally, pharmaceutical cold chains are complex and complicate processes because of requiring the involvement of many stakeholders with essential requirements. The pharmaceutical cold chain must provide multiple parties with the ability to update and share data. It also should be able to guarantee the validity of information, especially temperature ones, and secure them against human error and missing documentation. Therefore, it may interact with national and international verification systems, transport systems, and regulations. Most of the interactions are time-sensitive, but it is not always possible to manage the documentation quickly. Besides, during the transition, manufacturers, logistics companies, wholesalers, and pharmacists are not able to have complete visibility on the authenticity of medicine and its quality (Kapoor, Vyas et al.).

Private blockchains can help to solve some problems related to pharmaceutical cold chain data, such as data privacy, compliance, and cost and speed. If any doctor having access rights to that patient, then only that person should access their data. The data has taken by the doctor who has joined a blockchain network. They have no right to get their data without the patient's permission. This process causes to create a patient-centric approach. For keeping the safety of the real-time information, blockchain uses the cryptography algorithms such as RSA, SHA, and hash function where every block is jointed through a previous block and one specific random number that can be very hard to find by an intruder or attacker. In this way, blockchain can maintain the safety and privacy of the patient's data and get quality care at a very reasonable cost (Hathaliya et al., 2019).

Fig. 4 shows an overall blockchain structure in the pharmaceutical cold chain. Blockchain's effectiveness includes temperature monitoring, quality of products, the capacity of transportation, information, and management systems, storage quality, maintenance of cold chain equipment, product distribution, product management policies, and stock management (Mindila et al., 2019). This platform has many advantages in requirements of a pharmaceutical cold chain, which are Track-and-Trace, integrating extensive information, transparency in actor's communications, securing patient health data and IoT devices, avoiding counterfeit, helping researchers in genetic code unlocking, and generally, effective management of the pharmaceutical cold chain (Jochumsen and Chaudhuri 2018). In this section, the mentioned advantages are described separately.

3.1. Pharmaceutical serialization and traceability

Traceability has an important role in securing drugs and the basis for reliance on the part of the consumer in the pharmaceutical cold chain and its products. Traceability enables the pharmaceutical cold chain to verify the background of a product, keeping the path of all the places and the participators that deal with it. In the pharmaceutical cold chain, traceability would improve reliability among consumers and all the entities of the distribution pharmaceutical network. The necessary condition for its performance is that all the prescription drugs must identify quickly and fake drugs and counterfeit medicines withdraw from circulation. In the workflow of a pharma chain network process, before entering a new product into the distribution part, the pharmaceutical firm has to connect to a central verification all the serial numbers of the medicine package units that have been made and ready to be sent (Chiacchio, D'urso et al., 2019).

Safety and reliability of the drugs and their transactions throughout the life-time and distribution chain must be guaranteed by the central verification, although all parts (except patients) have to preserve some of these data for several years, especially the one related to their duty. Based on this approach, any of these participators is responsible for its information and for the coordination process with the central verification that must behave as a central authority (Chiacchio, D'urso et al., 2019).

Blockchain can be used to control the progress in preventing fraud. It also can handle and improve some features of the pharma cold chain as follows:

— Possession: every participator of the distribution part is responsible for a product once they get it.
— Unification: each box of drugs that can be sold separately must be identified by a unique serial.
— Information coordination: each part is responsible for the coordination process of their data with a central regulatory.

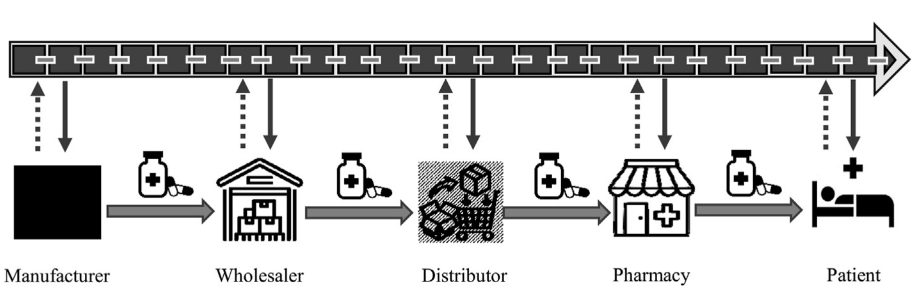

Fig. 4. Blockchain-based pharmaceutical cold chain management system.

— Information keeping: each part (except the patients) are called to preserve for several years the process information about the products controlled.

Fig. 5 shows the implementation of blockchain in the workflow of the pharmaceutical cold chain.

According to this workflow, it is possible to collect all this information and encrypt them into a smart contract of a blockchain. The smart contract that encrypts all the related information of the serialization process has to control and tight the traceability process along with all the distribution networks. Each time a new drug is packed, the blockchain server links to the smart contract to make an electronic identity of it that is saved and encrypted in the blockchain with all the relevant data.

Once the new data is registered to the blockchain, the smart contract can retrieve and update it by using the unique identifier allocated and used as a stamp with a Quick Response code (QR code). The only inner variable of the variable good that can be registered is a sequence of strings, named Status. Each time the owner requires to update some data about the status of the product, the sequence is developed such that all the history of the product is tracked. So, each time the product (pallet, case box, or unit box) has to be manufactured by the owner, the status data can be attached to the blockchain (Chiacchio et al., 2020).

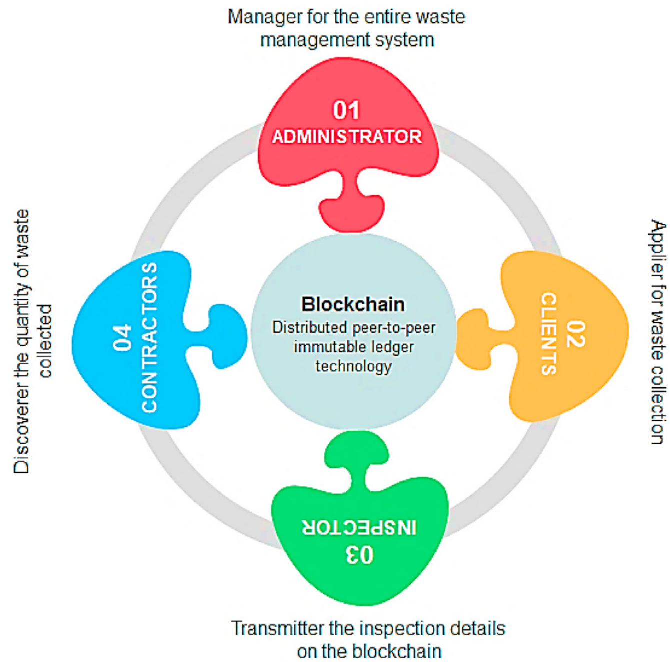

Fig. 6. Blockchain process in the pharmaceutical waste management system.

3.2. Pharmaceutical waste management

The process of managing waste includes all the activities that are done to manage waste from head to end. These activities according to the United Nations classified into three groups. The first group includes gathering, shipping, treatment, and disposal of waste. The second one consists of controlling, monitoring, and regulation the first group's actions and the last category entails the prevention of waste generation through the process of modification, reuse, and recycling (Ongena et al., 2018). Waste management is so important and it is the final aim for the supply chains. However, if waste is produced, then tracking is crucial for reasons related to the circular economy and industrial coexistence. It may also be significant from the aspect of waste disposal (Kouhizadeh and Sarkis 2018).

There are two major classifications of pharmaceutical waste: pharmaceutical waste that includes expired or unused drugs consisting of vaccines and sera that are disposed by domestic households and health care treatment industries and those pharmaceutical waste stemmed from hospitals and healthcare and research organizations (Rajbongshi et al., 2016).

Blockchain is also capable of dealing with minimizing pharmaceutical wastes. Fig. 6 presents the process of blockchain in pharmaceutical waste management.

As shown in Fig. 6, first, there will be a manager for the entire waste management system in the blockchain who is known as the administrator. In this platform, the clients can make their account in the blockchain and place their request for collecting the wastes from their homes. Each customer can enroll in the blockchain with essential information like name, address, and ID proof. Once the administrator approves the registration, the clients can access the blockchain. After the registration is fulfilled, the client can send the request for waste collection in the platform and join a document regarding the waste type and the place from where the waste will be gathered.

Different types of payment methods must be accessible along with a cash-on-delivery choice. The inspector transmits the inspection details on the blockchain and makes a profile on the distributed peer-to-peer changeless ledger platform. He also chooses a site for waste management and gets feedback form from clients and takes the necessary steps. The inspector transmits the inspection details on the blockchain and makes a profile on the distributed peer-to-peer changeless ledger platform. The contractors make their accounts in the blockchain and do the task gives to them by the municipality. The contractor's job is to discover the quantity of waste collected, and declare the details to the municipality. The municipality can also employ outdoor institutions like the police to find out in case any accident has happened and investigate the cause of the accident and report back to the municipality. Finally, it should be noticed that administrators are responsible for managing and monitoring everything in the blockchain platform (Mondal et al., 2019).

3.3. Pharmaceutical digital identity

One disease may be resulted from or related to another previous disease, hereupon the accurate diagnosis of the doctor is affected by the quantity and quality of the patient's medical information that is now available. Especially when previous diseases happened a long time ago and the patient forgets some details of it, such as the

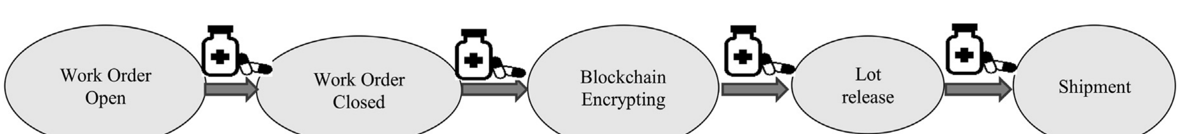

Fig. 5. The workflow of the pharmaceutical cold chain.

medicines or the medical examinations or when the patient cannot explain about elder diseases considering his/her poor medical knowledge. Both of these situations affect the judgment of the current doctor therefore, sometimes the doctor cannot deduce correct information for the diagnosis (Zhang and Lin 2018). Through the development of technology, electronic medical records replaced the paper documents related to the patient's health records and make them easy to carry, transform, save, and share. The most notable issue in this area is privacy preservation which means protecting reputations and benefits for the patients (Wang et al., 2019). Electronic medical records also help pharmaceutical scientists develop precise medicines based on having access to accurate integrated data (Fan et al., 2018).

Blockchain with its ability to keep an indecomposable, decentralized, and clear record of patient data makes a platform that is private and maintains the identity of individuals using complex codes protecting health information. Medical records are distributed in many different healthcare centers and so, they are difficult to access. Blockchain can enable patients to have full and secure access to all of their records and medical history which can be effectively referred by peoples involved in treatment (Griggs et al., 2018). This access can be confirmed using an encryption strategy to ensure security and privacy preservation (Fan et al., 2018). In this way, the blockchain leads to faster diagnoses and personalized care programs. The decentralized nature of it allows patients, doctors, and healthcare providers to share the information fast and securely as well (Haq and Esuka 2018). Besides, the authorized pharmacies will be able to view the medicine prescribes by the doctors to a patient and this subject promotes the advancement of precision medicine (Alonso et al., 2019). Hence, the digitalization of the chain leads to connecting these parties and reducing the paperwork (Shuaib et al., 2019). This technology also provides recording the effect of products on patients after the consumption to use for future statistics (Haq and Esuka 2018).

3.4. Pharmaceutical data integrity

The primitive advantage of blockchain technology is the ability to provide a single source of truth for chain actors. It ensures the agreement of participants about the nature of the data that have been sent to the network which is the main reason for their essential consensus. This advantage gives unique transparency to the network that omits the need for middlemen and also makes it ideal for industries having regular verification. It also improves the speed of decision-making regarding facilitating information flow and distrust. To solve this problem, the pharmaceutical chain requires a proper tracking mechanism in which no one can manipulate the drug information. Blockchain can solve this problem by providing a tamper-proof system accessible to multiple parties (Katuwal et al., 2018). The peer-to-peer network of blockchain, which relies on consensus algorithms to guarantee the security and consistency of any new block added, is called "tamper-proof transaction cryptography" (Bahga and Madisetti 2016). Each node in this distributed database maintains an upgraded copy of the database with all the ownership information and transaction history. The arrangement of blocks in the blockchain makes the transactions tamper-proof. Due to the connection of the blocks, any unplanned change in one block makes the network inconsistent. Therefore, it does not accept any changes caused by an attack in transactions of blocks (Pandey and Litoriya 2020).

Besides, pharmaceutical companies produce the medicines with codes concluding traceable details such as the name, location, timestamp, ingredients, usage of the drug, and side effect along with authorization by regulatory approval to keep the data integration at each stage and prevent drug with lack of codes enter to the system (Kumar and Tripathi 2019). Many pharmaceutical companies use holographic technologies to verify the originality of their drug and confront the fake medicine issue. But these types of packaging are expensive and also holograms may be cloned (Singh et al., 2020).

3.5. Pharmaceutical transparency

Blockchain technology can provide transparency to the pharmaceutical cold chain and considers the needs of the supplier, producer, logistics, distributor, and customer in the pharmaceutical cold chain (Surjandy et al., 2017). A blockchain could be applied to ensure that all pharmaceutical adheres to the maintenance of patient protection and smart contracts facilitate this process (Khezr et al., 2019). The smart contract, blocks, state database, and policies have shaped the node of the blockchain. The state database is applied to show and save the state of the ledger at a given point and time. All relationships of the node are indicated in Fig. 7.

As presented in Fig. 7, each ledger entrance shows the state relating to the drug data. Characteristics of the drug such as name, quantity, expiry-date are recorded with their values. The blocks consist of the transactions corresponding to drugs. The drug transaction would append to the ledger by verification policy. Policies are made based on node agreement. For example, AND ('Dept1.member', 'Dept2.member') and OR ('Dept1.member', 'Dept2.member') are two agreements. The first one is used when both parties must agree with the transaction and the second one is used when one part is must agree with the transaction (Jamil et al., 2019).

4. Case studies

Blockchain is a technology with numerous features that can solve the main problems of the pharmaceutical cold chain as discussed. These capabilities have been applied to solve different problems of the health and pharma systems. Several cases that attempt to solve problems of the medical and pharmaceutical systems with blockchains features are discussed in this section. Based on the characteristics of each platform and the main problem that has been addressed, the case studies are divided into two categories. The first group of cases including Pokitdok, Patientory, Medicalchain, Coral Health, Clinico mainly focus on manage and securely access to pharmaceutical and health information and facilitate the information sharing process. The second group of cases including iSolve, Curisium, Chronicled addressed the problem of counterfeit products in the pharmaceuticals industry.

4.1. Case 1: Pokitdok

Pokitdok presents platform-based blockchain in which a service is given to integrating healthcare organizations existing legacy systems. Pokitdokh develops a Platform-as-a-Service (PaaS) that provides healthcare organizations to quickly build modern commerce experiences among the healthcare value chain. Pokitdok uses "DoKchain" that creates a safe network like smart contracts for all sources of patient data, from Electronic Medical Records to medical devices and pharmacies (Katuwal et al., 2018; Antipova and Rocha 2019). First, Dokchain provides a secure validation management system for each party to participate in the transactions. Second, it can excuse independent auto-adjudication. It means that once the parties have been confirmed, the transaction is processed immediately in a machine-to-machine relationship based on agreed smart contracts (Miller 2017). The platform of Pokitdok permits users to join with over 700 trading partners and use a set of key-pairs for identity validation of the partner

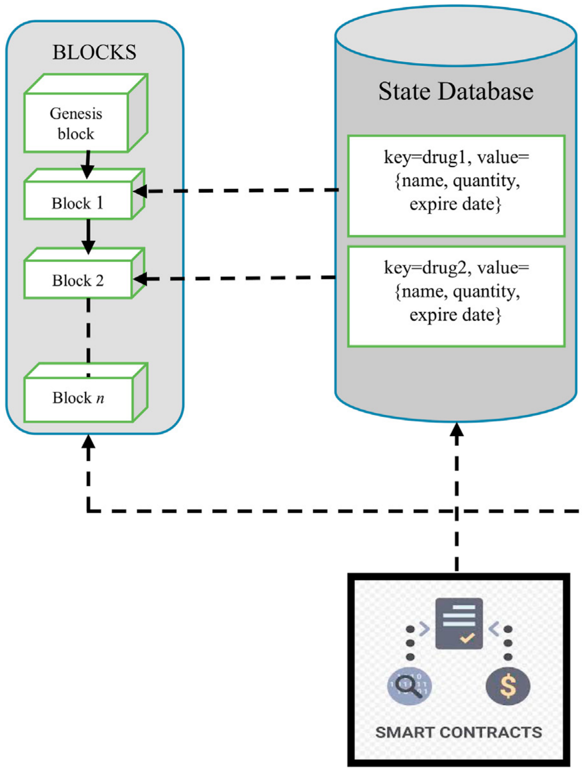

Fig. 7. Blockchain in a drug delivery pharmaceutical cold chain.

transactions which provide a secure and unaltered context. Also, they use the Proof of Elapsed Time (PoET) consensus algorithm in which security is ensured through a strong identity and constant notary of the stored data (Jahankhani and Kendzierskyj 2019; Onik et al., 2019). In summary, the process is performed in Pokitdok can be explained as follows: In the first step, some of the patient's information such as the patient's pharmacy insurance, plan number, prescribed medication, and the prescribing provider's National Provider Identifier (NPI) is gotten. Then, in a fraction of a minute, their Pharmacy APIs return computed out-of-pocket expenses, deductible and coinsurance information, extra plan scope limits, prior authorizations, refill quantity limits, or step treatment need (Cohen 2020).

4.2. Case 2: Patientory

The healthcare ecosystem has some issues such as: making clear patient healthcare information systems (PHI), electronic health records (EHR), and clinical data; increasing efficiency and decreasing spending; improving safety and doing changeless medical audits, and removing duplicate data and eliminating paper works (Upadhyay 2019). Patientory's blockchain-based system through Atlanta, Georgia, is used to solve these challenges. Patientory enables patients who want to be more connected to their health care documents. Especially for those with chronic diseases like diabetes, access to health documents will permit patients to preserve records of their health data and therefore have greater responsibility, availability, and control over their health and even for those consumers with a one-time medical issue like surgery, Patientory allows patients a way to quickly and effortlessly communicate to providers through their profiles. Also, medical professionals using Patientory to keep, store, and easily send safe medical data. It enables them to join other healthcare providers in the patients' network, permitting them to enjoy a more unified network and make the best kind of medical care to their patients. Moreover, they can chat with patients by the HIPAA (Health Insurance Portability and Accountability Act) compliant messaging system. Besides, many healthcare organizations are worried about information gaps. By applying Patientory's blockchain technology to save and send records, organizations can rely on experts for data safety (Brennan 2018). Patientory has presented a distributed application DApp in which Patientory's DApp connected blockchain technology, which is an open and safe technology that holds transaction records on blocks that are joined and saves them on a distributed and encoded database that works as a ledger. DApps are applications that join with blockchains that are not reserved or controlled by a single entity or in a single place. It means that a specific EHR or healthcare provider not only controls an individual's healthcare data but also permitting for more efficient, easy-to-use, and secure sharing of healthcare information across different providers and EHR platforms (patientory, 2019).

4.3. Case 3: Medicalchain

Physicians are faced with a large amount of information that is so hard to deal with them. A blockchain solution can facilitate this responsibility and also engaging the patient in their care (Engelhardt 2017). Technology company Medicalchain uses blockchain to make a user-centralized electronic health record and keep a single real report of the user's data (Albeyatti 2018). As a prime project, Medicalchain has coped with summaries of hospital discharge, which contains a summary of cure and essential follow-up care. Hospitals need to be sure about these documents that are free of liability-making mistakes and process them fast to free patients for the next one in the queue. Nowadays, sending documents over municipal boundaries can require a written plea, and problems with repetitive information, fraud, and inaccessible information are prevalent. Medicalchain has offered a digitized solution that conducts doctors through a structured discharge procedure that decreases mistakes and deletion and accelerates review by chiefs (Engelhardt 2017).

This system applies a dual blockchain structure, which will help efficient decentralized sharing of information between partners. The first one controls the availability of health documents and is created using Hyperledger Fabric. The second one is provided by an ERC20 token on Ethereum and contexts of all the applications for our platform. The Hyperledger blockchain, a permission-based network, needs participants to sign up to use it. This blockchain uses Hyperledger modeling and access control languages for controlling permission on a network. Hyperledger Fabric, as a distributed ledger platform, is based on a modular architecture with higher safety, resilience, and scalability. Medical information is so important in both social and legal sides, so a permissioned-blockchain such as Hyperledger Fabric helps to keep the necessary privacy needed for such a service. Hyperledger Fabric managing access to health evidence, as it has multiple layers of a license, it means that the owner of data can decide which parts of their data are available. Medicalchain also uses smart contracts to make digital health applications and services. These applications and services will be integrated use by the user's health information. Medicalchain team facilitates the health ecosystem to provide value, decrease costs, and finally modify people's lives (Albeyatti 2018).

4.4. Case 4: Coral Health

In the traditional healthcare system, all actors such as providers, laboratories, payers i.e. insurance companies and drug companies store patient data in various formats and therefore, there is no standardization in maintaining the records. Poor data sharing infrastructure causes data confusion in health records. Many other problems faced by the current healthcare system, including the siloing of data, the incongruity of legacy databases, the drawbacks of analyzing unstructured data, prohibitively high administrative costs, the lack of data security, and unaddressed privacy concerns can be handled by technologies such as blockchain. A Canadian, Vancouver based healthcare technology company focuses on problems of patients and doctors in lack of a platform to share patient's health information. Coral Health uses blockchain technology to facilitate sharing and getting access to patient's information easily throughout the system (Park 2018).

Its vision improves efficiency in interactions between key actors in the healthcare domain, driving productive data sharing, greater profitability, and improved public health outcomes. Coral Health ecosystem connects doctors, scientists, lab technicians, and public health authorities by putting patient information on distributed ledger technology that permits patients to easily and securely share their medical records with providers, labs, payers, and other stakeholders while keeping the privacy control of their medical information. It also uses the blockchain to accelerate the care process, automate administrative processes, and employ smart contracts between patients and healthcare experts to ensure data and treatments are accurate (Daley 2019).

The system is developed on the Ethereum blockchain and contains the Coral Health token and the Coral Health Ledger Smart Contract. The token is the standard ERC20 token contract on the Ethereum blockchain and facilitates the necessary economic exchanges between users of the Coral Health system. At the same time, the Coral Health Ledger Smart Contract will implement a database of all records that have been uploaded to the network and keeps a complete list of medical data files and an access control list. The Ledger will store only minimal metadata about medical data records, and actual records will be encrypted and stored off the blockchain (Park 2018).

Coral Health used InterPlanetary File System (IPFS) decentralized storage system which is a distributed file system for devices over the Internet (Li et al., 2019). It's a peer-to-peer protocol where each node stores a collection of hashed files and transfers the data digitally and securely overall connected systems (Health 2018; Dash et al., 2019).

The Coral Health ecosystem has also many benefits for pharmaceutical companies by improving the treatment study process and reducing administrative workloads. Its platform reduces clinical trial recruitment costs and enables pharmaceutical companies to evaluate the safety and efficacy of their treatments better.

Pharmaceutical companies can search the metadata stored on the Coral Health system to achieve potential sample sizes for their trial. They can request access to promising sample records and attract interested people to attend the desired test. Moreover, they can conduct retrospective analysis by searching the data of patients who have taken their medication the most, and recruit these individuals to participate in a study. Pharmaceutical companies have access to the full medical records of these participating patients to evaluate the success of their treatments and identify promising patients for expanded indications. The US Food and Drug Administration (FDA) often requires long-term assessments of treatment and access to participants' full medical histories provides an affordable way to study the long-term effects of treatments. Participating in the Coral Health ecosystem also reduces administrative costs for pharmaceutical companies by automating compliance reporting. They can also use Coral Health's smart contract platform for managing clinical trial adverse event reporting and save administrative costs spent on compliance reporting. This improves the quality of the information and increases the safety of future clinical trials (Park 2018).

4.5. Case 5: Clinico

Clinico is a US-based blockchain startup that uses blockchain technology to improve healthcare and pharmaceutical industries which is empowered by patients and enabled by blockchain. Clinico is a healthcare product with a digital patient record management system that enabled clinical trial patients to share, manage, and profit from their clinical trial data (CLINICO 2017). It allows patients across clinical trials to insert their data into one platform and researchers can achieve and use the data with informed consent using encrypted contracts. Patients then receive automatic payments whenever their data is used. Pharmaceutical companies benefit from patients' clinical trial data, but Clinico gives patients having control over their data. Every company is competing for market advantage and benefit from patients' data. They have access to limited data which makes their researches repetitive and expensive. Clinico aims to return the power equivalency from pharmaceutical companies to patients to create a market to empower sharing the data (Berkeley 2018).

4.6. Case 6: iSolve

iSolve was developed in May of 2014 to make stronger user networks and improve patient outcomes and safety (iSolve 2018). iSolve teams try to solve a common problem such as data accumulation and lack of data in Biopharma, Healthcare, Medical Device producer, and Life sciences industries. They have provided an Advanced Digital Ledger Technology (ADLT) platform to omit data silos by making a practical platform. This platform complementary existent systems and can also contain new technology like the

Internet of Medical Things (IoMT) and improve machine learning and big data. This platform can solve a vast variety of challenges like global supply chain track, R&D, clinical trials, and the movement of patient medical documents (case, 2018). ADLT also uses blockchain as the system to track, verify, and preserve all logistical movement of medications for developing the life cycle of the drug and drug supply chain in the biopharma and healthcare industry. Precise tracking is so important to preserve counterfeit and fraudulent drugs and medications. ADLT can control the life cycle from production to distribution by blockchain, therefore simple things such as expiry dates can be recognized with precision, and the probability of fraudulent relabeling of changing of dates decreases. iSolve can increase funds and improve drug development through Smart Market where data is kept safely and is trackable, unalterable, and visible as a marketplace to investors and service providers (Jahankhani and Kendzierskyj 2019).

Moreover, iSolve has a platform known as BlockRX that is incorporate blockchain technology and iSolve's ADLT. This platform is developed to improve patient outcomes by unifying the investigation of life science researchers, BioPharma firms, medical device producers, medical equipment retailers, and health care providers. The BlockRX Ecosystem for BioPharma makes new income flows and manages costs and enables safe access to data (Brennan 2017). The goal of BlockRX is joining systems that do not already connect and make data source that satisfies regulatory and commerce requirements. By focusing on making a network of Trusted users for facilitating the transmission of data (blockrx, 2018).

4.7. Case 7: Curisium

Curisium is a healthcare technology and services-firm-based in Manhattan Beach that incorporates Silicon Valley engineering with Wall Street big data analytics to make a cutting-edge blockchain platform for consumers, pharmaceutical manufacturers, and providers to enter into patient-oriented, safe, scalable, and efficient innovative contracting adjustment (Curisium 2019). Curisium can control a wide variety of data at a low cost. Their cryptographic systems assurance that data is only used for its predesignated and permitted purposes. Curisium platform is fully compliant with HIPAA and General Data Protection Regulation (GDPR), and their blockchain preserves an automated survey sequence of all activities. In addition, the Curisium health state-based data model permits complicate patient-level contracts to be created briefly, readable, auditable manner (Curisium 2019). In combination with secure and trustful computation technologies, the Curisium platform provides the basis for payers, providers, and life science companies to automate patient-centered, value-based contracts and reducing counterfeiting drugs, and increasing transparency about the costs.

Furthermore, Curisium has some benefits in the financial sector for its users. The Curisium's blockchain-based system provides a single source of truth to decrease disputed claims of medical rebates. Any claims can be solved fast and efficiently. Throughout the dispute process, the platform creates full visibility and position tracking. The platform consists of quantitative analytics to help users improve clinical outcomes while decreasing costs. Moreover, users can evaluate their benefit decisions and tracking efficiency immediately and simulate their plans to gain profit through Managing their risk for each drug group (Curisium 2019).

The payer perspective was ignored in the traditional budget impact methods and their value and utility were limited. Cognition and attention to the payer's unique perspective are very prominent to make the financial model for the payer. Curisium addresses this limitation by determining the clinical and financial impact of a given product to the payer's specific members. Although commercially accessible data sets in the health and pharma sector have some problems such as often incomplete, vague, inflexible, and not validated, Curisium solves these issues by making precise, validated data sets that are fully customized to the users' requirements (Curisium 2019).

4.8. Case 8: Chronicled

Since 2019, FDA welcomes the project proposals that propound solutions to meet the 2023 requirements of the Drug Supply Chain and Security Act (DSCSA). DSCSA is created to improve the security of the pharmaceutical supply chain in eliminating counterfeit pharmaceuticals and enhancing patient safety (MediLedger 2020). A person may return counterfeit drugs that are inadvertently resold by the manufacturer or wholesaler. Therefore, in the regulation of DSCSA, all products must have a serial number to be verified as authentic when they are returned (Morris 2018).

Chronicled, a San Francisco-based blockchain startup is a software technology company leveraging blockchain for making a supply chain more reliable, efficient, and automatic. It provides tools and protocols for multi-party supply chain ecosystems using decentralized blockchain networks. This decentralized network developed the boundaries of trust and enforces trade rules among the organization by keeping private data. The company is also active in the Pharmaceuticals industry supply chain. Privacy and security protocols of this network help pharmaceuticals enterprises to protect and automate their supply chains, simplify business processes, and reduce operational costs (Chronicled 2019).

In 2017, Chronicled created the Mediledger Project which is a ledger system assigned to the safety, privacy, and efficiency of pharmaceutical supply chains. MediLedger is a consortium of leaders from 25 pharmaceutical companies that launched the blockchain-based compliance protocol as a solution to the 2023 DSCSA requirements (Kshetri 2018; MediLedger 2019). Chronicled uses a lighter and faster consensus algorithm compared to public Ethereum setup and zk-SNARKS which is a form of zero-knowledge cryptography that ensures full privacy parties and blockchain commercial scale (LedgerInsights 2019).

MediLedger intends to be the industry consortium to deal with serialization and other commercial problems of supply chains. Blockchain is a good tool for pharmaceutical serialization and tracing because of its ability to be an identical source for sharing information securely between many parties. The decentralized feature of MediLedger's blockchain makes the data stores on multiple separate servers and makes data manipulation so hard. Even if one server is hacked, it's so hard to manipulate other server's data. Pharma service providers and even individual companies can use MediLedger's solution for their products (Morris 2018). Chronicled provided a track and trace tool for the pharmaceutical industry (Prnewswire 2017).

4.9. Case 9: COVID-19

Currently, humanity is the witness of growing and increasingly complex changes in the world. A timely and effective response to these changes is an essential challenge for governments and nations all around the world. The outbreak of COVID-19 is one of these challenges in the 21st century that put the mobility and capability of health system states to a great test (Bedford et al., 2020; Bamakan and Haddadpoor jahromi, 2021). The effect of the COVID-19 pandemic and its consequences are reflected in every corner of our daily life, businesses, global economy, people's movements, and totally the way of interacting with each other and the world. Different vaccines have been approved against the coronavirus, while each has its specific supply chain condition. In fact, cold chain management involves ensuring that extremely temperature-sensitive coronavirus vaccines are maintained at the correct temperature during the production, storage, transportation, and distribution processes. Vaccine cold chain management will necessitate varying degrees of collaboration and cooperation among a variety of stakeholders.

Several various technologies in computer sciences such as Artificial Intelligence, Virtual and Augmented reality, IoT, Healthcare trackers, wearables and sensors have been utilized to cure the disease such as AIDS, EBOLA, etc (Singh et al., 2020). As the case of coronavirus, the need for a system that can ensure reliable and secure transfer of clinical information along with the parties that are not controlled by a single centralized authority, or a single government. In fact, it is unavoidable for the countries to share their experiences to manage the spread of the COVID-19 virus properly. Blockchain technology can ensure tamper-proof information sharing due to its unique features in terms of information sharing like reliability, security, anonymity, and decentralized approach (Abd-alrazaq, Alajlani et al., 2020; Bamakan et al., 2021). With the expansion of the Internet of Medical Things (IoMT) that includes bio-sensors, medical gadgets, and their communications technologies, healthcare systems would significantly empower in the prevention and combating of the COVID-19 (Dai et al., 2020). However, these systems intrinsically suffer from security and privacy issues that blockchain technology enables them to deal with these problems. Furthermore, blockchain-enabled IoMT provides effective solutions to issues such as tracing the pandemic origin, quarantine and social distancing, smart hospitals, medical data provenance, remote healthcare, and telemedicine (Dai et al., 2020; Kalla et al., 2020).

Moreover, blockchain distributed ledger technology can be used to increase integration across entities in a safe manner. Three highlighted features may be provided by using blockchain transactions across entities:

(a) Immutability as health information saved in the blockchain ledger cannot be changed as this will be registered with the new hash values,
(b) Transactions can be modified by most of the nodes in a decentralized network and
(c) Analysis of the ledger transactions cause traceability

Furthermore, smart contracts can be made based on the blockchain and permit automated contractual agreements through some pre-defined features. To sum up, the benefits of blockchain usage in traceability, immunity passport, and COVID-19 recognition, and other health scenarios help to combat the pandemic (Abd-alrazaq et al., 2020).

5. Discussion and challenges

As discussed in the literature, more focus is required on blockchain usage in pharmaceutical cold chain management. This study addressed blockchain applications in the pharmaceutical cold chain with the view of developing its management and solving the obstacles mainly presented in Fig. 8.

Despite the advantages described, there are also some challenges in using blockchain in the pharmaceutical cold chain as shown in Fig. 9.

5.1. Security and privacy of data

In the blockchain, all transactions are confirmed by all parts of a community instead of one relied on the third party so the information sent by one node can be accessed by all nodes involved in a system (Raj et al., 2019). Therefore, the data feces to potential privacy and security risks. The lack of a third party for approval needs the patient in the pharmaceutical cold chain to select one or more representatives that can get his information and medical history on their behalf. Now, this representative can further permit a group of people to gain records of the same patient, which may make a large number of data privacy and security threat. High-security systems taking part in the data will cause barriers in transmitting the data from one block to another and, thus, the receivers will have to get the limited or incomplete information. Moreover, a kind of safety breach may happen in blockchain networks that are known as a 51% attack. This attack includes a group of miners that possess more than 50% of the blocks in a blockchain network. The miners get authority over the network and could prohibit any new transactions from happening by not providing them with admission (Siyal et al., 2019).

5.2. Storage capacity

Another challenge that may occur in blockchain-based systems is the storage capacity problem. Blockchain was created to maintain and process the transaction data, which has a limited scope, so it does not require heavy storage. With time, as it developed into the domain of the pharmaceutical cold chain, storage challenges became to appear (Siyal et al., 2019). In these chains, there is enormous medical data, images, documents, and lab results and it needs a significant space for saving all these types of data. Every node in the blockchain network has a copy of all records, this can cause a lack of storage space of current blockchain technology (Ullah et al., 2020). Also, usages of blockchain are transaction-based, and therefore the databases used for this technology tend to rise at a rapid rate. The increasing size of databases causes the speed of record-searching and -accessing becomes decrease, which is highly inappropriate for the kinds of transactions where speed is crucial (Siyal et al., 2019).

5.3. Uncertain development cost

To build and manage a traditional pharmaceutical system for information storage and data exchange needs to spend a large amount of time, human resources, and money along with it. Also, there are additional costs of continuous system updation. Blockchain system may be reduced this cost, but the cost of establishment and keeping of pharmaceutical records using blockchain is unknown to many of the organizations and no one can accept the technology without knowing the exact cost and expenses (Raj et al., 2019; Ullah et al., 2020).

5.4. Standardization

As a pharmaceutical cold chain is related to human life, to implement blockchain in this system successfully there should be a suitable way of data storage of patients' health record and information exchange between different systems takes part in blockchain application (Raj et al., 2019). International standardization authorities should create several well-authenticated and certified standards. These predefined standards should be useful to evaluate the size, data nature, and format of the information exchanged in blockchain applications. These standards will not only scrutinize the shared information but also must apply as a precautionary safety action (Siyal et al., 2019).

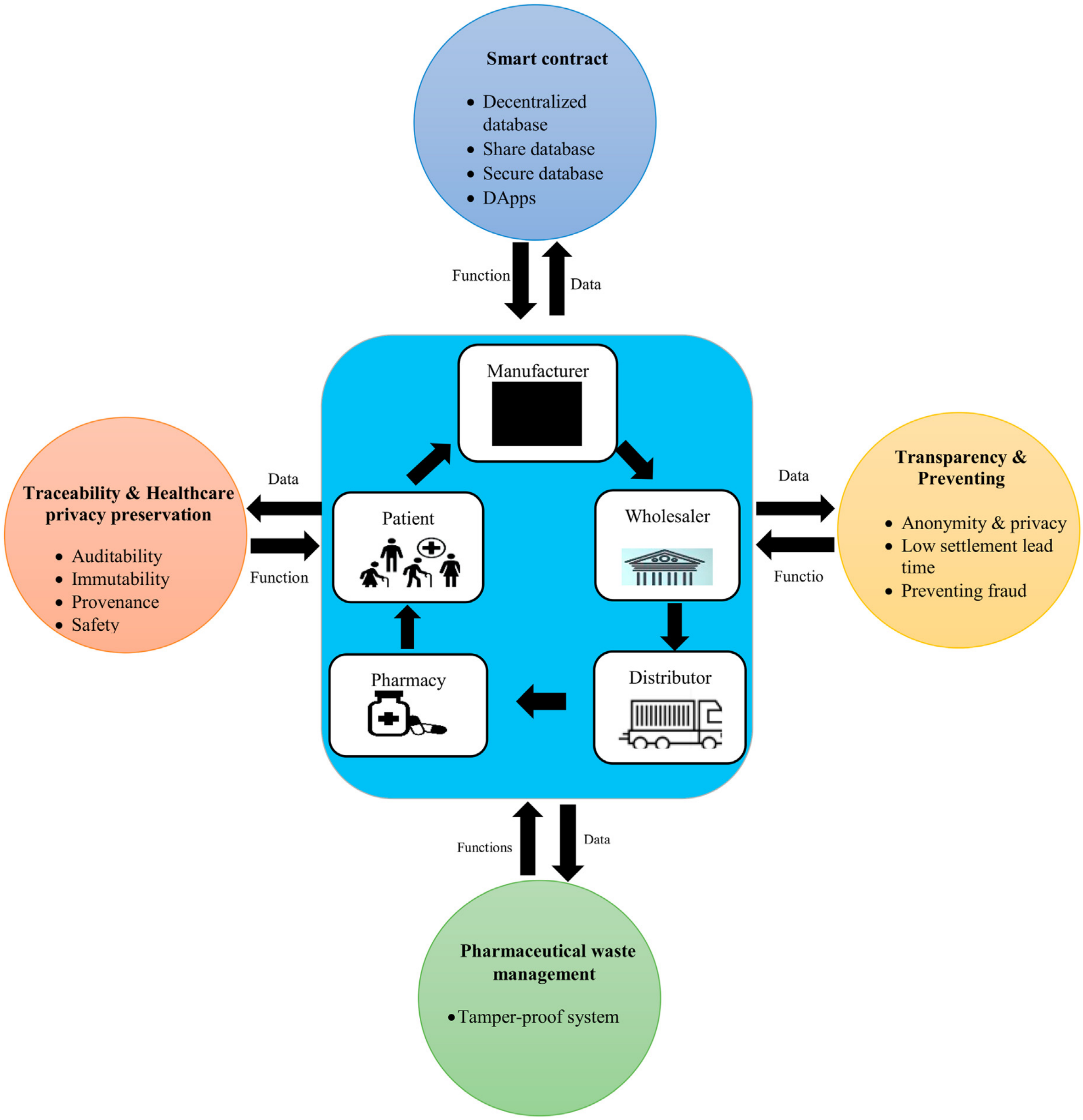

Fig. 8. Blockchain-enabled pharmaceutical cold chain advantages.

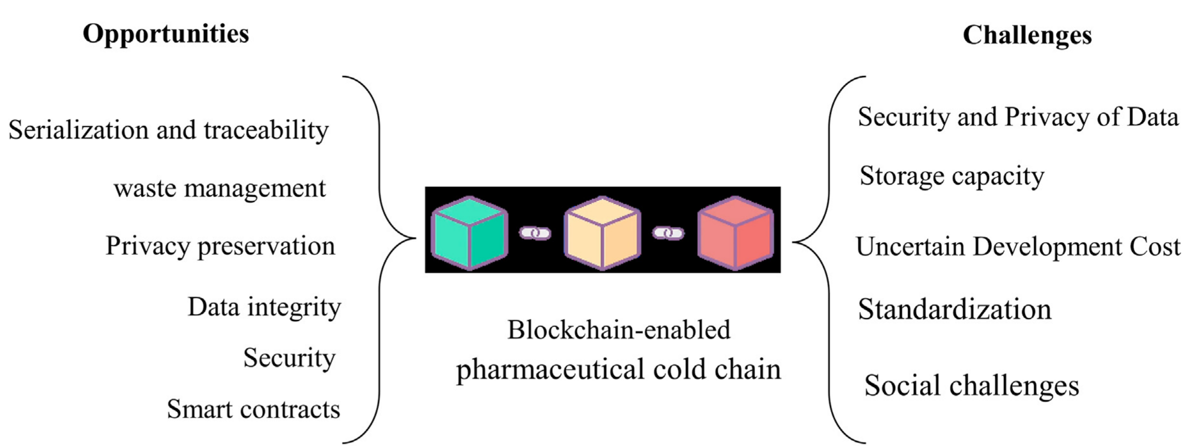

Fig. 9. Opportunities and challenges of blockchain-based pharmaceutical cold chain systems.

5.5. Social challenges

Blockchain technology is still progressing and therefore meets social challenges such as a cultural shift. Accepting this technology that is so different from the traditional work methods never comes easy. Although the pharmaceutical industry is slowly moving towards blockchain, it takes a long time to use this technology completely. Most patients do not like to share their data with multiple participates, so probabilities of cultural resistance may happen. To use blockchain in this system some efforts will need to change the behavior of the people so they will admit data sharing in a distributed environment (Raj et al., 2019; Siyal et al., 2019).

6. Conclusion and future work

The pharmaceutical cold chain has processes that are likely to be controlled efficiently by blockchain technology. Blockchain would benefit the pharmaceutical cold chain by bringing data integration, secure transactions, serialization, and traceability. But there are major problems in the adoption of blockchain in the pharmaceutical cold chain yet, that are required to be considered. In this paper, we discussed the main benefits and drawbacks of the pharma cold chain and provided some cases that employed blockchain features in their projects. Despite all the advantages that blockchain brings to pharmaceutical cold chain management, there are still challenges that need to be overcome.

In the following, we present some main areas where future research could investigate in the domain of blockchain-based pharmaceutical cold chain. First, future research could focus on the potential adoption of smart contracts in the pharmaceutical cold chain. This might facilitate customer service through more efficient data exchange between different parts of the pharmaceutical cold chain.

Although a smart contract is applied to the transparency of the pharmaceutical cold chain, there are still several limitations to be coped with. These limitations can be classified into four groups based on the smart contract's life cycle. These groups are creation, deployment, execution, and completion which are explained below.

— Creation challenges: contract creation is the main phase in the performance of smart contracts. Participants have to code their contracts and then extend them to diverse blockchain platforms. Codes of the smart contract are registered in different programming languages such as Solidity and Java. So, different types of programs will be executed in different periods, and make these programs readable in each type is a great subject.

— Smart contract platforms have several problems in functional issues such as re-entrancy and block randomness. Re-entrancy happens by interrupting function and recalling securely again. Evil participants may use this weakness to rob currency. Block randomness occurs in some cases such as lotteries and betting pools in which generating block randomness happened. This can be done by producing pseudo-random numbers in a block timestamp or nonce. Some evil miners may create some blocks to deviate from the outcome of the pseudo-random generator. By the way, hackers can control the probability distribution of the outcomes.

— Deployment challenges: deploying a smart contract on a blockchain will be done after the creation of it. Extension of a smart contract on a blockchain may face some issues such as contract correctness and dynamic control flow.

— Execution challenges: execution of a smart contract occurs after deploying it (Zheng et al., 2020). In this phase, some problems may happen like lacking trustworthy data feed and Transaction-Ordering Dependence (TOD) in execution. When a smart contract gets data from external resources for execution, the trustworthiness of the data can not be assured. Transaction-Ordering Dependence (TOD) occurs when some dependent transactions that happen in the same contract are placed in one block in the wrong order. It can cause malicious attacks during the execution of a smart contract (Wang et al., 2018).

— Completion challenges: After the performance of a smart contract, the regulation of the system state will be accumulated as a transaction and extended to each node (Zheng et al., 2020). However, the increase of smart contracts creates some problems. One of the most important ones is privacy issues. When all transaction is saved on the blockchain and is shown to anyone, users private data can be gained by investigating transaction graph structures and it is called deanonymization attack (Wang et al., 2018).

Second, the nature of blockchains would certainly preserve information from being changed or stolen, but the sensitive data might end up being sold to third persons for questionable marketing aims, and those might still be indirectly identifiable by fakes identifiers or patterns of information. Since information safety plays a crucial role in the pharmaceutical cold chain, future research could pursue designing protocols for managing private cryptographic keys for network nodes.

Moreover, other future research trends could focus on how different blockchain-based pharmaceutical cold chains would cooperate and interact with each other. So, interoperability and cooperation are significant issues.

Blockchain interoperability is the ability for disparate blockchain systems to easily communicate with each other without too high investment costs and share, exchange data, and access information across different blockchain networks without the need for an intermediary. This property of blockchain reduces the time spent on administrative tasks, entering duplicate data, waste, cost of verification, and finally increases the validity of the product's information by allowing parties to agree about the shared data (Gordon and Catalini 2018). The applicability of the blockchain in the pharmaceutical cold chain depends on the cooperation and coordination of all relevant parties and stakeholders. The role of IT knowledge of actors is effective in this subject. The personnel involved might be required to be re-trained on blockchain technology if they want to use the blockchain (Katuwal et al., 2018). This makes blockchain easier to use and faster.

Finally, as the system's participants and its transactions increased, the problem of scalability is more visible. It is more deals with blockchain's infrastructure. The more types and numbers of pharmaceutical products entering into the system, the more computational space for smart sensors and devices are needed. Especially when there is a need to monitor the product information in detail, a large space and considerable power are used to perform computation throughout the network. Here the cold chain requires smart devices that are equipped with more computing power and higher speed to be able to properly use the capabilities of the blockchain. Otherwise, they may not run at their full potential or may cause blockchain malfunctions (Hussien et al., 2019).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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