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№ 11601

Application of Blockchain Technology in Pharmaceutical Closed-Loop Supply Chain: a Literature Review

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December 21, 2023

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***Abstract*— Environmental and social concerns have prompted many industries, especially healthcare product supply networks, to improve sustainability in the Supply Chains (SC). Indeed, the evaluation of triple bottom line concepts becomes critical in Closed-Loop Supply Chains (CLSC), as its operations are primarily targeted toward sustainability objectives. Moreover, the rapid evolution of modern technologies has altered the structure of CLSCs, prompting numerous companies to collaborate with e-commerce entities such as online platforms for both sales and recycling processes. Hence, a critical imperative exists to build a comprehensive framework integrating technological innovations to increase transparency, trust, and traceability within CLSCs. Meanwhile, Blockchain Technology (BT) can create an advanced database, ensuring the secure storage of product provenance information increasing efficiency, transparency, and sustainability. In this context, this review paper investigates research on blockchain-based CLSC, with a specific emphasis on applicability and features, specifically directed towards the digitalization of the pharmaceutical industry. The comprehensive literature review ultimately shows that the integration of BT in CLSCs is still in its nascent phases, and further research is required to conduct a mathematical analysis of its effects on both forward and reverse logistics within the system. Indeed, despite the significant potential of BT to address conventional challenges in an industry, there is a notable deficiency in research regarding its implementation in the pharmaceutical CLSC.**

I. Introduction

In recent years, the global COVID-19 pandemic has posed several challenges impacting people's lives, environmental protection, and the tactical and operational business processes, especially in Pharmaceutical Supply Chains (PSC). In this industry, manufacturers bear the pivotal responsibility of producing essential medical products and ensuring their efficient delivery to customers [1]. In this context, considering that end consumers within this critical industry are patients, the main objective of a PSC is to ensure timely and uninterrupted delivery of medicines [2]. However, due to the fluctuations in demand for pharmaceuticals, the complex network of stakeholders in medication delivery infrastructure, and the lack of real-time visibility and information sharing among partners, PSC management has been challenging in ensuring seamless forward logistics [3]. On the other hand, another pivotal challenge within this critical industry, often overlooked by researchers, is reverse logistics and the management of surplus or unwanted medicines within the PSC. Unwanted medicines include pharmaceutical products that have reached their expiration date, remain unused, or have been contaminated, and due to their potential safety concerns, these products require appropriate disposal procedures [4]. Hence, the inefficient collection and improper disposal of unwanted medicines in PSCs can harm human health and pose environmental risks, contributing to increased Greenhouse Gas (GHG) emissions and the contamination of aquatic ecosystems [5]. In this particular area, pharmaceutical enterprises endeavor to establish a closed-loop system to meet sustainable objectives, which are environmental concerns, social responsibility, and economical objectives. Indeed, a Closed-Loop Supply Chain (CLSC) can yield a 50% reduction in costs compared to previous operational processes and facilitate an 80% decrease in GHG emissions [6].

Nevertheless, the healthcare sector faces various obstacles and challenges, resulting in a diminished efficacy of pharmaceutical CLSCs in both forward and reverse logistics. Moreover, the rise of online shopping has been accelerated by the COVID-19 pandemic in recent years, which has led many firms in SCs to establish online sales channels in different structures. In 2022, global e-commerce sales reached US$5.7 trillion, marking a 9.7% increase and constituting 19.7% of the overall global retail sales [35]. However, the online sale has introduced a new challenge for the PSC. For instance, as estimated by the World Health Organization, approximately 10% of medicines in circulation are considered substandard, while close to 50% of drugs available for purchase online are identified as counterfeit [7]. The uncertainty cannot be denied and occurs in various stages of CLSC, from technical and operational activities to patients' preferences and behavior, which can create serious risks resulting in many disruptions in the whole system [8]. Indeed, the absence of cooperation among PSC members and stakeholders, along with the lack of transparency and visibility in healthcare sectors, constitutes fundamental factors contributing to elevated disease progression, drug resistance, and mortality rates [9]. In light of this consideration, pharmaceutical industries should enhance their data management systems to address prevailing disruptions and mitigate information asymmetry in the pharmaceutical CLSC [10].

Henceforth, new modern technologies have the potential to enhance information-sharing capabilities within data management systems, thereby mitigating additional costs, enhancing transparency, ensuring security, and improving

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sustainability in CLSCs [11]. Certainly, Blockchain Technology (BT) establishes a sophisticated database for the secure storage of medical provenance information, and the integration of this modern platform with other Industry 4.0 technologies enhances the tracking capabilities within the pharmaceutical CLSC, ensuring improved efficiency and transparency [12]. Given the growing attention and successful application endeavors in various industries like automotive batteries, energy, and food industries, there is significant potential for integrating BT in the pharmaceutical sector. Therefore, the enhanced data transparency provided by BT can increase trust between pharmaceutical CLSC members in various stages, including drug delivery, collection and recycling procedures, documentation, and overall end-to-end visibility [13]. Furthermore, BT can be strategically implemented to systematically record information regarding pharmaceuticals, tracing their processes from the initial production stages, involving raw materials at manufacturing sites, to their ultimate delivery to patients through various distribution channels. Moreover, the capabilities of BT can combat drug counterfeiting, which is a significant challenge in the world, and build trust between PSC and patients [14]. Nevertheless, in alignment with the previously mentioned statements, there is currently a notable absence of a literature review addressing the integration of BT within the CLSC processes. Therefore, this paper aims to undertake a comprehensive literature review on adopting this modern technology to find the research gaps. Furthermore, this study gives practitioners and researchers a good understanding of BT impacts in PSC based on closed-loop policies.

II. RESEARCH METHODOLOGY

To comprehensively examine relevant studies, searches were performed on Scopus and Google Scholar, in which Boolean operations employing 'OR' and 'AND' were utilized to link different terms. The specific selection of search strings applied in this paper is shown in TABLE I. It is worth noting that employing game theory approaches within the pharmaceutical CLSC is crucial in addressing the complex challenges inherent in this industry. It can provide a strategic framework that aligns the interests of diverse stakeholders, contributing to overall efficiency and sustainability. Therefore, using game theory approaches such as the Stackelberg game and Nash equilibrium is the basis of research selection for a literature review.

TABLE I. SEARCH STRINGS USED IN THE PAPER..

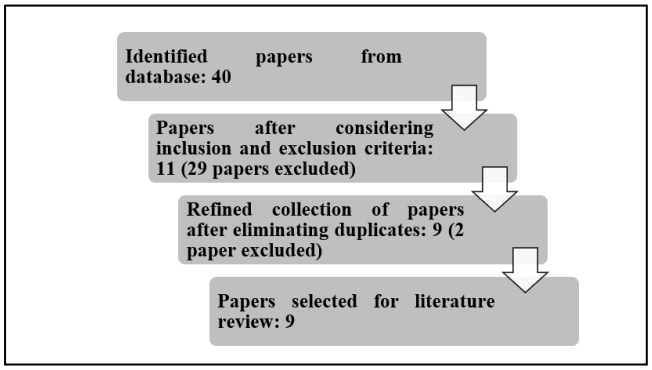
Keywords	Search strings
Blockchain	"Blockchain technology" OR "Distributed ledger"
	AND
Closed-loop Supply Chain	"Closed-loop supply chain" OR "Closed-loop system" OR "Pharmaceutical closed-loop supply chain" OR "Healthcare closed-loop supply chain"

TABLE II. INCLUSION AND EXCLUSION CRITERIA.

Criteria for Inclusion	Criteria for Exclusion
• Language Requirement: Studies included in this review must be written in English. • Source Type: Journals.	• Absence of a proposed mathematical model in the paper. • Mathematical model without considering game theory approaches. • Duplicated articles.

The selection of research for this publication has been conducted based on specific inclusion and exclusion criteria, as shown in TABLE II. This process led to the selection of nine studies, as the primary outcome of the review, as illustrated in Figure 1.

Figure 1. *Selection process*



III. LITERATURE REVIEW

Nowadays, SC activities such as manufacturing, transportation, warehousing, and material disposal have a greater impact on global warming, extreme weather, and disasters. Consequently, the importance of ensuring the sustainability of these operations has emerged as a significant global concern, particularly within the pharmaceutical industry [15]. In accordance with the principles of sustainability, resources should be utilized to meet present requirements without compromising the ability of future generations to fulfill their own needs [16]. Therefore, SC sustainability has provoked academic literature, and researchers are discussing various aspects of it, including strategic and operational processes. In this context, a CLSC helps to approach the system's sustainability principles so that economic goals, environmental concerns, and social performance are achieved simultaneously [17]. Nevertheless, a review of the literature indicates that only a limited number of papers have delved into the analysis of the pharmaceutical CLSC, in which the forward logistics of PSC has attracted more attention in the existing literature. For example, Hosseini-Motlagh et al. (2020) considered a pharmaceutical CLSC with one manufacturer and two retailers, in which there was a competition downstairs to collect the plastic drug containers by improving the corporate social responsibility efforts. The manufacturer reused these plastic drug containers to reduce operational costs in the SC, and he/she invested in research and development activities to produce more environmentally friendly products [18]. In another study, Hua et al. (2019) examined advertising and points-exchange incentives within a reverse logistics system for collecting unwanted medicines. Their findings emphasized that coordination mechanisms are crucial factors influencing the improvement of the collection rate in PSC [19].

A limited amount of research focused on establishing an efficient CLSC system for collecting and recycling unwanted medicines, encompassing both prescription and over-the-counter drugs. Furthermore, the structures of CLSCs have undergone transformations due to the global development of the Internet. Consequently, the realm of global online retailing on e-commerce platforms has garnered significant attention.

E-commerce can make the pharmaceutical CLSC smart by providing customer interaction and feedback or automated order processing in forward and reverse logistics. However, there is a significant gap in the literature concerning examining e-commerce within the CLSC. Nevertheless, implementing an efficient pharmaceutical CLSC based on sustainable objectives, whether in traditional or online sales formats, faces numerous challenges and critical issues that require careful consideration and resolution.

On the one hand, the CLSC depends on several factors because it involves complicated tasks such as collecting and inspecting unwanted or used products, recycling or remanufacturing operations, etc. [20]. Moreover, uncertainties within the PSC can amplify the complexity of managing operational processes, and inadequate control of uncertainty and inaccurate parameter estimations may hinder the sustainable development of the system [21]. Uncertainty in the CLSC can lead to a shortage of precise data and information. This inherent lack of accuracy can complicate processes and relationships among entities, posing challenges in making optimal decisions [22]. Considering the rapid growth of modern technologies globally, the digitalization process presents pharmaceutical stakeholders with more opportunities to attain sustainability in the closed-loop system suffering uncertain conditions. Moreover, it offers viable solutions for addressing challenges in establishing a trusted data management system [23]. Among these modern technologies, BT is the most famous platform for SC digitalization to improve system transparency, traceability, data immutability, and data privacy [9]. Despite the significance of technological innovation in CLSCs, particularly within pharmaceutical logistics systems, a few numbers of papers have undertaken mathematical investigations into the role of BT in enhancing the tactical and operational processes of the CLSC.

A detailed literature review has been conducted in this paper, and as illustrated in Figure 1, it is apparent that only nine papers have explored the role of BT in CLSCs. In this regard, TABLE III shows the existing papers on the implementation of BT in CLSCs. Moreover, the main decision-making variables of these papers have been carefully analyzed and illustrated in TABLE IV.

TABLE III. LITERATURE ON THE USE OF BT IN A CLSC UTILIZING GAME THEORY APPROACHES.

Papers	Channel structure	Sustainability			Channel Coordination	Blockchain technology effects				
		Economic	Environmental	Social		Transparency	Traceability	Trust	Information sharing	Token incentive
[24]	s	*	*	*		*		*		
[25]	s	*	*	*		*	*			
[26]	s	*	*				*			
[27]	s	*	*	*		*		*		
[28]	s	*	*	*						*
[29]	s	*	*		*			*	*	
[30]	s	*							*	
[31]	s	*			*		*		*	
[32]	s	*	*	*				*		

s: single channel, d: dual channel, m: multiple channel

TABLE IV. LITERATURE ON THE USE OF BT IN A CLSC UTILIZING GAME THEORY APPROACHES: DECISION VARIABLES

Paper	Pricing strategies for products sale	Pricing strategies for products collection	Collection and recycling efforts/ratio	Sustainability (green degree, social welfare)	Promotional effort	Brand goodwill	Order/selling quantity	BT service subsidy	BT investment level	BT traceability level	BT information trustworthy level
[24]	*		*		*	*		*			
[25]	*		*		*	*					
[26]	*	*								*	
[27]	*		*		*						
[28]		*	*	*							
[29]	*						*				*
[30]		*					*				
[31]							*		*		
[32]	*			*			*				

The reviewed papers are analyzed in the next section to find the most critical research gaps in adopting BT in CLSC management.

IV. ANALYSIS AND DISCUSSION

This section conducts a comprehensive analysis and discussion through various subsections.

A. Integration of BT across diverse industries

First of all, a noteworthy observation in Table III is that there is a significant gap in the exploration of CLSC management within the pharmaceutical industry, with a notable absence of research that provides mathematical analyses on technological innovations in this vital industry, particularly with respect to BT. For example, traceability information based on BT was discussed by Xing et al. (2022) to improve recycling strategies for automotive batteries in the CLSC. They indicated that adopting new modern technology can give stockholders more opportunities to increase their profitability [26]. Moreover, in terms of sustainability, the waste recycling process of electronic products was examined by Wang et al. (2022) to improve sustainability in the CLSC, and the impact of BT to build a traceable framework and resolve the inconsistency between the actual and theoretical recycling amounts was investigated [25]. In another paper, Yang et al. (2023) analyzed the role of BT in increasing trust among CLSC members and end consumers to convince them to purchase remanufactured products. They concluded that implementing technological innovation can help companies collect used products more efficiently. The findings of this study proved that the integration of BT can positively impact social welfare, e-waste recycling rates, and contribute to economic development within the CLSC [30]. Nevertheless, despite the growing interest in implementing BT in CLSCs, the pace of research growth pertaining to this modern technology in PSCs remains relatively slow compared to other industries.

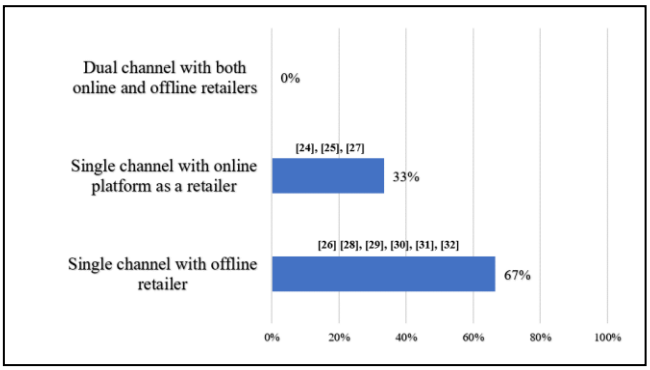
B. BT and e-commerce in pharmaceutical CLSCs

Moreover, another key area that requires clear analysis is the examination of channel structures. It is noteworthy that the current body of research in CLSC management lacks investigations into the role of BT within a dual-channel scenario involving both e-commerce platforms. For example, Ma et al. (2022) investigated the role of BT for recycling used products and the choice of sales format on an online platform to attain triple sustainability in a single CLSC. Their conclusion confirmed that technological innovations are fundamental in establishing a collaborative partnership between manufacturers and online platforms to increase profitability and recycling rates [27].

On the other hand, the PSC has witnessed ongoing advancements in the e-commerce domain, especially after the COVID-19 pandemic. In fact, since online platforms can provide convenience in space and time, they are becoming increasingly popular among end customers in the SC [36]. Therefore, many firms in SCs are seeking to establish online sales channels in different structures, including direct channel, reselling, and agency selling formats, both in forward and reverse logistics [37]. It highlights the importance of digitalization to address inherent challenges within traditional e-commerce systems, such as payment disputes, chargebacks, fraud, and a deficiency in transparency. Therefore, BT can be employed to create a decentralized network, providing a secure framework for pharmaceutical stakeholders and patients to share and collect trusted information about the medicine's origin and source, thereby mitigating the risk of fraud.

Nevertheless, the literature review conducted in this paper indicates that the utilization of BT in a dual-channel CLSC, specifically considering e-commerce in healthcare systems, is still in its nascent phases. Figure 2 illustrates the percentage of reviewed papers in TABLE III that address the role of BT on online platforms in the CLSC.

Figure 2. *Examination of e-commerce in CLSCs*

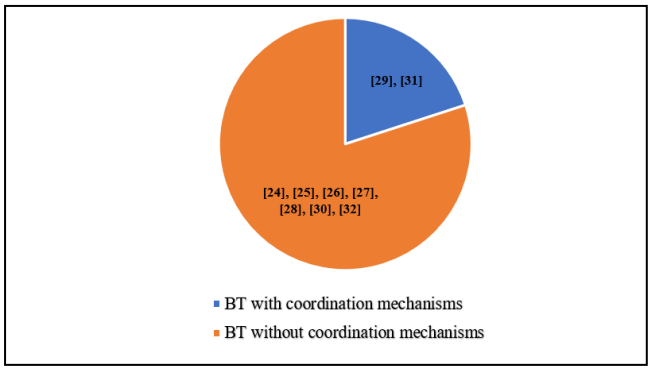


C. Cooperation in CLSCs after BT adoption

On the other hand, despite the fact that coordination mechanisms can provide enterprises with more opportunities to increase the sustainability and efficiency of CLSC systems simultaneously, according to Table III, the literature on this topic is very scarce. In fact, in the decentralized structure known as traditional decision-making, individual profitability is the priority of each company, which may harm the entire SC [33]. Moreover, a centralized structure is an ideal decision-making system with only one global organizer to make all decisions in the SC, and it is not common in most realistic scenarios [34]. Given that increasing profitability and sustainability are two primary objectives within the PSC, companies can gain significant advantages by utilizing coordination mechanisms as strategic measures to enhance the efficiency of BT implementations.

In this case, Salikhov et al. (2023) investigated the impact of BT on improving consumer satisfaction by providing information-sharing systems in a CLSC. The important result derived from this paper is that they utilized a contract mechanism to guarantee the effectiveness of BT investment in the system. They concluded that the cost- and revenue-sharing contracts can lead to a win-win outcome for both the supplier and retailer and have positive environmental implications [29]. Therefore, in the pharmaceutical industry, an examination of coordination mechanisms in conjunction with decentralized and centralized decision-making structures can provide more insightful results regarding the relationships between companies and the influence of BT in CLSC. However, it is clear from Figure 3 that existing literature has given limited attention to this crucial concept.

Figure 3. *Coordination mechanisms in CLSCs after BT adoption*

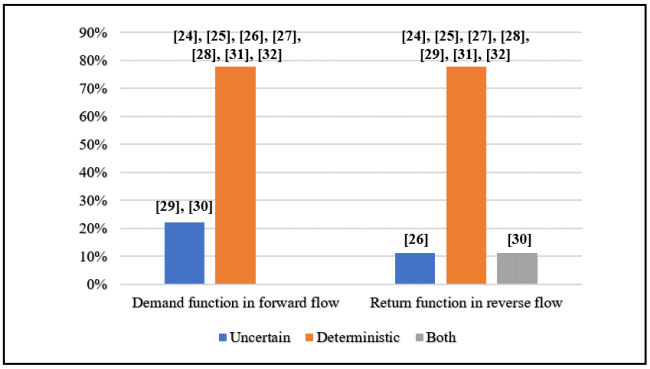


D. The role of BT in eliminating uncertainty in CLSCs

Nowadays, adapting the CLSC systems to handle all kinds of uncertainties is significantly necessary. For instance, uncertainty in market demand is a distinctive characteristic of PSCs in which customer requirements and the marketplace are unpredictable. Therefore, the lack of transparency and reliable information among stockholders in the PSC can contribute to extreme fluctuations in the market and complicate optimal decision-making on product pricing, inventory control, and sustainable concerns [35]. Different approaches to coping with uncertainties, such as dynamic, probabilistic, and stochastic programming methods, are utilized in the forward SC.

Still, the literature suffers from the lack of appropriate models to handle the uncertainty in CLSCs. Information asymmetry and the lack of trust among stakeholders can lead to higher uncertainty in the pharmaceutical CLSC. In this regard, digitalization can help companies cope with various uncertainties. However, as shown in Figure 4, there is a huge gap in modeling and eliminating uncertainty with BT adoption in the CLSC. More research is needed to mathematically illustrate the effects of uncertainty in various industries.

Figure 4. *Considering uncertainty in CLSCs*



D. The impact of BT on decision-making in CLSCs

Table 2 provides clear evidence that only a limited number of papers have undertaken mathematical investigations into the role of BT in enhancing the tactical and operational processes of the CLSC to enhance environmental protection and social responsibility. For example, the token incentive model under BT is considered by Li et al. (2023) to combat the unqualified recyclers in the CLSC. However, although the incentive scheme was able to increase social welfare in the system, it was costly for the manufacturer and negatively affected profitability [28].

From another point of view, despite the decision variables in these studies focusing on pricing strategies, none of them delved into the potential advantages of incorporating smart contracts into the system. Indeed, each company within the CLSC wants a secure network that does not necessitate a central authority to encode business rules. In this context, BT facilitates all transaction protocols through the utilization of smart contracts, which can be applied in many industries to increase trust among entities [38]. In the CLSC system, smart contracts play a crucial role in recording the prices of used products, overseeing end consumers' collection and purchase processes, and facilitating the seamless sharing of pertinent information across the network [39].

Regrettably, existing literature has devoted insufficient attention to scrutinizing the role of these innovative technologies and their distinctive features in CLSC management, particularly within the pharmaceutical industry. It is imperative to acknowledge that implementing BT and smart contracts is a complex task that requires a comprehensive analysis of their respective advantages and disadvantages.

V. Conclusion

Nowadays, end customers express a growing interest in acquiring comprehensive information about the origins of the products they consume. This includes details about raw materials, operational processes, recycling activities, and entities involved in the system. In this context, in response to the rising environmental awareness among consumers within the SC, numerous companies are actively pursuing strategies to enhance sustainability. Embracing CLSC is viewed as a crucial step to elevating collection and recycling rates. It is noteworthy that before formulating tactical and operational strategies for developing a decision support system, a critical step involves updating CLSC structures. Indeed, with the rapid expansion of Internet access and advancements in cutting-edge smartphone technologies, significant changes have occurred in customer purchasing behavior. Consequently, companies should collaborate with online platforms to enhance their marketing initiatives. Indeed, consumers are eager to access comprehensive product details, such as the product's origin and source, in order to mitigate the risk of fraud when making online purchases. However, the acquisition of counterfeit products in the PSC poses significant risks and can have severe consequences for people's lives. Therefore, technological innovations can serve as effective solutions for stakeholders to address consumer awareness and traceability concerns in a dual CLSC involving e-commerce platforms and traditional retailers. Indeed, BT stands out as a prominent platform for system digitalization, offering an advanced database mechanism that facilitates transparent information sharing within the CLSC. Moreover, stakeholders can leverage a smart contract, an electronic transaction protocol under BT, to digitize their payments, fulfill legal obligations, and enforce agreements without intermediary third parties.

However, the literature review presented in this paper highlights a significant gap in the utilization of BT within the CLSC, particularly in the pharmaceutical industry. Certainly, establishing a reliable data management system through integrating new modern technologies in PSC can simplify the decision-making process. This ensures the timely and accurate delivery of high-quality medicines to the intended patients. Furthermore, implementing a blockchain-based CLSC can enhance medical companies' understanding of the complexities surrounding medicine returns. This, in turn, facilitates the effective execution of medication take-back programs within the system. This approach assists the pharmaceutical CLSC members involved in e-commerce platforms to gain a deeper understanding of uncertainties and precisely make crucial decisions. Finally, it can be concluded that due to the critical role of BT applications in CLSC and the potential challenges within the healthcare product supply network, there is an apparent deficiency in mathematical models capturing the current state of this issue and its future development.

Furthermore, for future research, an in-depth analysis of the primary challenges identified in this paper can be undertaken, incorporating the principles of the circular economy and its integration with new modern technologies in CLSC management.

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