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STRENGTHENING PHARMACEUTICAL SUPPLY CHAIN SECURITY IN EUROPE: SERIALIZATION AND EMERGING TECHNOLOGIES

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Abstract *The pharmaceutical industry's profitability has attracted attention, but it faces challenges from counterfeiters exploiting vulnerabilities worsened by globalization and complex supply chains. In 2019, European authorities introduced regulation EU 2016/161 to enhance drug supply chain security and traceability. By conducting a systematic literature review, this study assesses the effectiveness of the European Drug Serialization system, examining its implementation and the potential benefits of integrating digital technologies like RFID and Blockchain. The aim is to investigate and identify measures contributing to the strengthening of pharmaceutical supply chains against counterfeiting. The research suggests that while serialization is crucial, it may not provide foolproof security, emphasizing the need for additional digital technology integration.*

Keywords *Counterfeit Drugs, Digital Technologies, Blockchain, Pharmaceutical Serialization, RFID.*

1 INTRODUCTION

The pharmaceutical industry has been known to be a highly lucrative and profitable business. The global pharmaceutical market is estimated to be around $1,5 Trillion (Gonzalez Pena et al., 2021). Along with its profits also come big challenges, especially when the stakes are high. The importance of life-saving drugs along with complex global manufacturing and supply processes makes it more vulnerable to various external forces trying to benefit from the possible lapses within the system (Mackey et al., 2015). The impact could be high and devastating both for the industry and for the patients. In this paper, we investigate the effectiveness of the Drug Serialization system implemented in Europe through a literature review and explore potential enhancements by integrating emerging technologies like Radio Frequency Identification (RFID) and Blockchain to combat counterfeit drugs.

The pharmaceutical industry has been constantly trying to create an environment where it can ensure safe delivery of drugs to the patients but with multiple global manufacturing sites and fragmented supply chains (Rosseti and Handfeild, 2011), the operational complexities also increase. The pharmaceutical supply chain, comparatively to other industries, is far more complex and challenging (Argiyantari et al, 2020). The pharmaceutical industry, characterized by intricate logistics and an extensive supply chain (Pedroso and Nakano, 2009), faces a multitude of challenges. Beyond the evident business and economic concerns, these intricacies can also pose severe risks to the ultimate beneficiaries – the patients. These

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risks encompass issues such as supply delays, drug shortages, and the circulation of counterfeit medications (Blackstone et al., 2014), all of which can have devastating consequences for the well-being of patients. The major challenges that the industry is continuously facing are maintaining the overall visibility of its products, having uninterrupted supply lines to avoid delays and losses, detecting thefts or unexpected movement of products, and above all ensuring the health professionals and patients receive the drugs in time (Kochan et al, 2018). It is of utmost importance that the correct flow of technical information and protocols is respected. The pharmaceutical industry's strong global demand for pharmaceutical drugs, coupled with substantial investments and complex supply chain structures, increases its vulnerability to counterfeit drugs. (Jarrett et al, 2020). The 2020 OECD/EUIPO report points out that "the weak links in fragmented global supply chains allow counterfeiters of pharmaceuticals to succeed".

The current focus of the European authorities (as well as other global healthcare authorities) is on the implementation of serialization of pharmaceutical products throughout the EU member states. Serialization in the pharmaceutical field is a system that ensures the secure monitoring and verification of pharmaceutical products as they move through the supply chain (Pascu et al., 2020). The potential for track and trace and the ability to verify products throughout the entire supply chain were the major forces behind serialization (Nabiyeva and Wu, 2017). Track and Trace refers to the ability to follow and control a product throughout its lifecycle until it is delivered to the final user (Chiacchio et al., 2022). However, the European system is not a complete track-and-trace system as their partial involvement in the verification procedure leaves it up to the national authorities to decide how to regulate (Valcheva, 2021). Serialization enables the verification of the authenticity of the product (Rasheed et al., 2018) but may not be able to completely track the product on its own. Despite global efforts to implement pharmaceutical drug serialization, the latest worldwide figures on counterfeit incidents concerning pharmaceuticals have shown an increase of 38% from the year 2020 to 2021(PSI, 2022). This is of big concern as the highest numbers have been reported from North America. It is to be noted that both the US and Europe have already implemented their serialization regulations in their respective territories. This present central system is flawed and falls short of meeting all the requirements for the deployment of effective anticounterfeiting techniques (Chiacchio et al., 2022). Experts are arguing that pairing the current drug serialization with the latest digital technologies such as the Internet of Things (IoT) and Blockchain would eventually result in a full-proof track-and-trace system securing the drug supplies by providing precise monitoring and better management throughout the pharmaceutical supply chains including reverse logistics (MG et al., 2019; Raijada et al., 2021; Saha et al., 2022).

While pharmaceutical drug serialization has been adopted by numerous countries, including those in Europe, it remains uncertain whether the current system provides a foolproof track-and-trace solution for the industry. Limited research exists regarding the effectiveness of the European authorities' current serialization system. By analyzing relevant literature, this paper delves into the implementation of the European Drug Serialization system and assesses possible improvements by integrating emerging technologies like Radio Frequency Identification (RFID) and Blockchain to bolster the battle against counterfeit drugs. The paper also assesses both the advantages and reservations surrounding these new technologies.

2 METHODOLOGY

The primary objective of this research article is to evaluate the implementation of Drug Serialization and investigate the prospective advantages of incorporating digital technologies for the enhancement of traceability and administration within pharmaceutical supply chains. This study entails a comprehensive systematic literature review to evaluate the efficacy of the Drug Serialization system as instituted by European regulatory authorities, as well as to investigate the potential advantages derived from the integration of digital technologies to fortify pharmaceutical supply chains against counterfeit activities.

The review encompasses the analysis of prominent journals and industry reports, utilizing authoritative academic databases including SCOPUS, Web of Science (WOS), and Google Scholar.

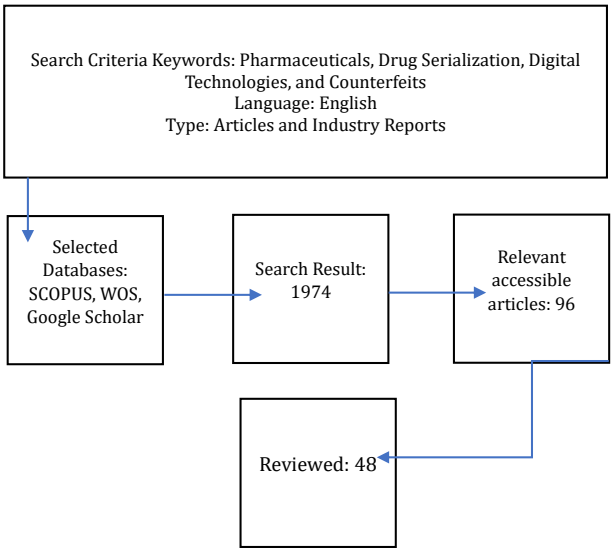

Fig 1: Search Approach for Identifying Articles. Source: Authors

The figure provides an overview of the research aimed at identifying and reviewing articles related to pharmaceuticals, drug serialization, digital technologies, and counterfeit drugs, with a focus on academic articles and industry reports, without a specific limitation on publication years. Initially, the search generated 1,974 outcomes, of which 96 articles were identified as pertinent based on their titles. Subsequently, following an assessment of the abstracts, 48 articles were subjected to a more comprehensive examination, as they met the criteria.

Tab. 1: Articles Reviewed; Source: Authors.

Category	Number of Articles	Authors
Drug Serialization	19	Chiacchio et al., 2022; Kootstra and Klienhout-Vliek, 2021; Markarian, 2014; Nabiyeva and Wu, 2017; Nalam, 2023; Pagonidis et al, 2020; Parmaksiz et al., 2020; Pascu et al., 2020: Piper, 2019; Pisa and McCurdy, 2019; Rajora, 2022; Rasheed et al., 2018; Rivers, 2022; Sarkar, 2022; Stobie, 2016; Sturtevant, 2017; Valcheva, 2021; Whyte, 2017; Widengren, 2017
Digital Technologies **(Blockchain)** **(RFID)**	21 (11) (6)	Abugabah et al, 2020; Acierno et al, 2010; Alharthi et al, 2020; Chircu et al, 2014; Gupta et al., 2021; Haddara and Staaby, 2018; Jochumsen and Chaudhuri, 2018; Kshetri, 2017; Kshetri, 2018; Mackey and Nayyar, 2017; Mettler, 2016; MG et al, 2019; Patton, 2006; Raijada et al., 2021; Saha et al., 2022; Sylim et al., 2018; Yao and Li, 2010; Yao et al., 2012; Yli-Huumo et al., 2016; Zakari et al., 2022; Zheng et al., 2017

Drug Counterfeit	8	Bansal et al, 2013; Deisingh, 2005; Glass, 2014; Mackey et al, 2015; Nayyar et al,2019; OECD/EUIPO, 2020; Soon and Manning, 2019; You et al., 2016

The table classifies a range of research articles into three distinctive categories in the pharmaceutical field. The "Drug Serialization" category encompasses 19 articles, spanning from 2014 to 2023, focusing on the monitoring and authentication of pharmaceutical products in supply chains. In the "Digital Technologies" category, 21 articles (comprising 11 articles on blockchain and 6 articles on RFID) explore the application of digital solutions to enhance pharmaceutical operations and security. The "Drug Counterfeit" category includes 8 articles examining strategies to combat counterfeit pharmaceutical products and their implications for public health. This categorization provides a comprehensive overview of the diverse themes and research areas within the pharmaceutical industry, addressing serialization, digital technology integration, and the challenge of drug counterfeiting.

3 COUNTERFEIT DRUGS

In this section, the discussion is rooted in the findings of our literature review focused on the issue of counterfeit drugs. Fake medicines or counterfeit products pose a big threat to the healthcare industry and a huge challenge to the authorities (Nayyar et al,2019). They are deliberately and fraudulently produced products that can have disastrous consequences on patients worldwide (WHO, 2018). Counterfeit medicine is defined by the European Medical Agency (EMA, 2021) as "a medicine made by someone other than the genuine manufacturer, by copying or imitating an original product without authority or rights". According to WHO, counterfeit medicines account for 50% of the overall global drug trade (Glass, 2014). The study conducted by OECD/EUIPO suggests that the number of children dying from pneumonia every year after receiving counterfeit drugs could be as high as 169,000 (OECD/EUIPO, 2020). Recently, Interpol launched Operation Pangea XIV involving police, health, and customs authorities from 92 countries wherein they seized 9 million COVID-19-related products worth USD 23 Million and closed 113000 illegal websites (Interpol, 2021). The Pharmaceutical Security Institute (PSI), a non-profit organization dedicated to pharmaceutical crimes has been recording incidents related to counterfeiting, thefts, and illegal diversions.

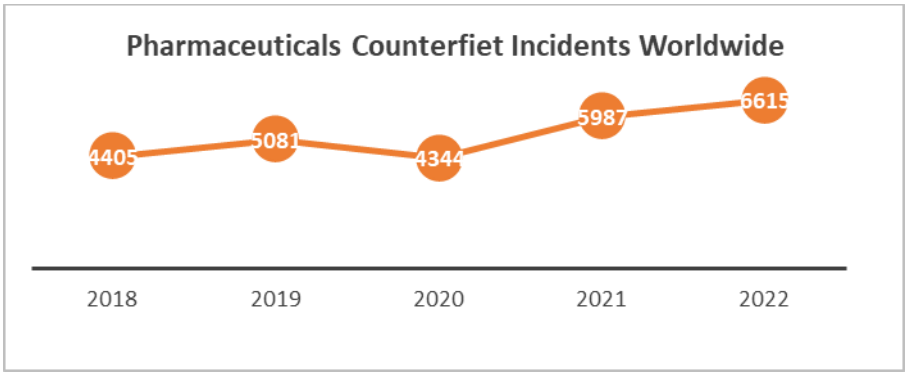

Fig 2: Pharmaceutical crimes recorded per year by PSI; Source: www.psi-inc.org/incident-trends.

As per their records, the number of criminal incidents, despite all the efforts by the industry, has been alarmingly growing in the past few years. 4405 reported incidents in 2018 to 6615 in the year 2022 (PSI, 2022). These are only the cases that have been recorded by PSI, but the real figures could be far more.

The efforts to put a full-proof traceability system have been on for a long within the pharmaceutical industry and the objectives have been very clear i.e., to ensure full visibility, safety, and timely and authentic supplies of drugs to the healthcare professionals and patients. Various techniques have been used by companies for authentication of their products such as holograms, security inks, tamper tamper-proof seals but they have been unable to be fully potent against counterfeits as consumers may fall prey to the fake ones (Markarian, 2014). Such technologies that are used on packaging to authenticate the products are stand-alone and are not fully integrated within the system and remain exposed to counterfeiters (Soon and Manning, 2019). Industry requires a system where it can have full visibility and control of its products – right from manufacturing up to the delivery to the patients and vice versa, in case of returns or product recalls. More robust technologies such as barcoding, RFID, and blockchain are being favored to track and trace the products by the industry (Kootstra and Klienhout-Vliek, 2021).

4 SERIALIZATION

Serialization involves attaching a digital history and a distinct code to a drug package, enabling tracking and authentication through barcode scanning (Pascu et al., 2020). The literature review shows that numerous health authorities globally are adopting it to strengthen their pharmaceutical drug supply chains. The global compliance for drug traceability is moving towards drug serialization, as more countries adopt and standardize their regulations (Rajora, 2022). Bar codes and 2D Data matrix have been standardized in the pharmaceutical industry and has been extensively explored in the relevant literature. Companies use it to identify and trace their products and it includes useful information concerning the product and the company. Bar codes are one-direction vertical lines and 2D codes are two-dimensional barcodes represented in a square form. The information can easily be accessed by a mobile phone or an optical reader. As compared to the barcodes, the 2D codes are superior and have more advantages as they are smaller and can accommodate more information (Diazgranados and Funk, 2013).

The application of 2D codes on pharmaceutical products has become mandatory by EU healthcare authorities since 2011. The EU Falsified Medicine Directive (FMD) 2011/62/EU required data matrix codes on the secondary packaging including product code, batch number, and expiry date (EUR-Lex, 2011). These measures were taken for better transparency and traceability of the products. Having product details on secondary packaging did help the purpose but had certain limitations as the traceability of the singular saleable unit within the secondary packaging remained elusive. The European authorities issued regulation EU 2016/161 to further strengthen the traceability and transparency throughout the supply chain of pharmaceutical drugs by adding additional security features by serializing items to the unit level or individual packs (European Commission, 2016). In the efforts to restrict the entry of counterfeit drugs into the legal supply chain and for identification and authentication, the directive required safety features by placing UI (Unique Identifier) and anti-tampering devices on the packaging of certain medicinal products for human use (Stobie, 2016). This was in parallel with similar efforts taken by the FDA in the US where the Drug Supply Security Act (DSCSA) required all pharmaceutical companies to serialize by placing a product identifier on individual packages (Sturtevant, 2017). The time for the companies to comply in the US was till 2017 and further increased to 2018 whereas in Europe was February 2019, three years from the issue of the directive.

Fig 3: Illustrative example of GS1 2D Data Matrix barcode; Source: Authors

The European Commission's requirement for the serialization of medicinal products demands a unique identifier composing the product code, serial number, National Healthcare reimbursement number or identification number(optional), Batch Number, and Expiry date. The European Pack Coding Guidelines recommend the utilization of GS1 standards. GS1 is a global organization maintaining the Global Trade Item Number (GTIN) system and barcode standards that are used to identify items (GS 1, 2021). The product code consists of (GTIN) allocated to each item and must have a code length of 14 digits. The serial number is unique per product and consists of 20 alphanumeric digits (EMVO, 2017). The National Healthcare Reimbursement Number is optional depending on the requirement of the national competent authorities of the member states and if not printed elsewhere on the packaging. The requirements for the batch number and expiry date remain the same (European Commission, 2016).

The advantages of serialization seem to be enormous, however, our literature review shows that its implementation can be challenging. Traceability can be achieved by technological advancements, but it also requires the political willingness and commitment of governments. In low or lower-middle-income countries, political barriers along with corruption could hinder the implementation of such technologies (Pisa and Mcurdy, 2019). Operational issues such as handling and management of serialized products with non-serialized ones within the warehouse and consigning the products to markets where regulations and requirements could be different as per the local laws could be challenging (Pagonidis et al., 2020).

The key challenge for the pharmaceutical industry in the implementation and integration of serialization in its full supply chain operations, as underscored in the literature, has been its financial implications (Widengren, 2017). The investment can be significant for companies exposing some of the low-cost companies, especially the generics manufacturers losing their competitive edge and making them more vulnerable to price competition. Data integration and IT have been of concern as they require homogeneity among manufacturers and all the software-related service providers for the smooth integration of a large amount of data (Chen et al, 2020). Further, labeling on individual bottles and vials could pose a challenge due to their size and curvature (Jarrett et al, 2020). However, it leaves them with no choice other than respecting the regulations if they want to operate in the regulated world. With such additional costs, pharmaceutical companies can have higher visibility of their products and can convey their commitment to a safe, transparent, and uninterrupted supply of products. Though the present literature recognizes that serialization undoubtedly is a crucial part of the pharmaceutical track-and-trace system, it also acknowledges that it may not be a full-proof solution for securing pharmaceutical drugs (Nabiyeva and Wu, 2017; Valcheva, 2021; Sarkar, 2022) as the current European requirements do not make aggregation mandatory as part of its current system (Piper, 2019; Rivers, 2022). Aggregation pertains to the connection between the original package and each subsequent container or package employed for transporting a saleable unit (Whyte, 2017). Serialization enables the verification of the genuineness of a product but may not be able to verify the quality or track the product throughout the supply chain (Parmaksiz et al., 2020; Pisa and McCurdy, 2019). To bolster security and clarity, it is essential to develop unit-level tracking (Sarkar, 2023) which would enable wholesalers, distributors, and dispensers to access interconnected electronic data at the individual unit level (Rajora, 2022; Nalam, 2023).

In the current complex supply chain process, as outlined in the literature, serialization is used in tracking systems that are vulnerable to tampering because embedded codes have fixed values that can be easily altered and tampered with by counterfeiters (Gupta et al., 2021). The tracking and tracing of each drug

package along the supply chain from the manufacturer to the consumer is the goal of serialization and the pharmacies are required to inspect each package that is sold, and manufacturers are required to register new packages at the central database managed by the European Medicines Verification Organization (EMVO) which could be compromised and exposed to the forgers (Schraml et al., 2018). Further, in the recent variation of the European track-and-trace system based on the serialization and verification of prescription drugs, Delegated Regulation (EU) 2016/161, excludes wholesalers from obligatory verification unless there are exceptional circumstances with a greater risk of falsification (European Commission, 2021; Valcheva, 2021).

5 RFID

Radio Frequency Identification (RFID) systems, which are being recommended for pharmaceutical distribution and return management, promise highly coordinated and controlled systems of inventory management across all distribution and retailing channels (MG et al, 2019). Radio Frequency Identification (RFID) technology has been used for years in many industries and seems to have grown with time. The use of electromagnetic waves to transmit and record electronic data automatically without any interference makes this technology attractive (Yao et al., 2012). Electronic tags can be attached to pharmaceutical products to efficiently manage and track them throughout the supply chain process (Mackey and Nayyar, 2017). The FDA has been encouraging its use since 2004 to counter illicit drug trade and secure the supply chain of the pharmaceutical industry. Big industry giants such as Pfizer have been investing in it to secure their blockbuster products (Patton, 2006) and many companies are using them for tracking their cold chain products. However, the industry seems hesitant to adopt and standardize it globally (Abugabah et al, 2020). Technically advanced countries are moving towards RFID whereas Europe seems to be more favorable for implementing 2D barcodes (Bansal et al, 2013).

As identified during our literature review, there could be many reasons for the reluctance towards RFID technology in the pharmaceutical industry. Insufficient awareness among organizations could be one of the reasons behind its slow penetration (Haddara and Staaby, 2018). Some believe the electronic tags may affect the quality of biological products (Acierno et al, 2010) or may cause some interference with the equipment in the hospitals (Yao et al., 2010). Another reason is the high cost related to the implementation of such technologies. The tags are expensive (Deisingh, 2005) and for low-value products, it may not be an attractive option. Further, questions are raised on the reliability of the tags as their reusability can threaten the safety of the stored data (You et al., 2016). There are concerns highlighted in recent literature that electronic tags are vulnerable to manipulation and can be cloned (Alharthi et al, 2020; Raju et al, 2020). IoT applications and platforms' reliance on a centralized cloud system can be a major security flaw (Kshetri, 2017). The use of RFID technology in the pharmaceutical industry will continue to grow as it offers many advantages over barcoding from visibility to traceability to end users however it is essential to keep in mind that RFID technology on its own will not result in improvements unless the processes it supports and the appropriate allocation of human resources are also altered appropriately (Chircu et al, 2014). With further advancements in technology, we should see how RFID technology evolves and becomes more robust and economically feasible for all the stakeholders involved in the pharmaceutical supply chain process. However, Blockchain has the potential to track products throughout every party in the supply chain and throughout their product life cycle, which means that in the long run, it may also render track and trace by IoT devices obsolete (Jochumsen and Chaudhuri, 2018).

6 BLOCKCHAIN

The quest for securing global pharmaceutical supply chains by introducing a viable full track-and-trace system within the pharmaceutical industry starting from the raw materials, and manufacturing to the supply of safe and reliable products to the end users (Chiacchio et al., 2022) has been the highest priority for global healthcare authorities. With the global COVID-19 pandemic, emerged the need for digitalization

of businesses and industries. The literature review shows that Blockchain Technology has high potential in securing and strengthening drug supply chains. The assessment of current and emerging technologies for combating counterfeit drugs identifies blockchain as a promising solution, offering the potential to track and trace pharmaceuticals and verify supply chain participants for effective counterfeit detection (Mackey and Nayyar, 2017; Sylim et al., 2018). In the pharmaceutical industry, it is believed that moving forward, this technology in conjunction with product serialization could provide a solution for a foolproof track-and-trace system throughout the entire supply chain of pharmaceutical products (Chiacchio et al., 2020). Many researchers have recently turned to blockchain technology as a means of transmitting data through drug supply chains because conventional systems can easily have their data deleted, altered, and tampered with (Zakari et al., 2022).

Blockchain Technology is a distributed ledger that allows recording transactions in an effective, permanent, and verifiable manner (Zakari et al., 2022). Blockchain is a decentralized solution that does not necessitate a middle organization (Yli-Huumo et al., 2016. Blockchain's core attributes, including privacy, decentralization, immutability, and the capacity for scrutiny, have showcased its potential to revolutionize traditional sectors (Zheng et al., 2017). Due to the inherent features of blockchain technology that guarantee decentralization, immutability, privacy, and data security (Mettler, 2016), the pharmaceutical industry seems possibly the most exciting and preferred beneficiary of the digital revolution (Chiacchio et al., 2020). In contrast to IoT devices which are vulnerable to hacking and manipulation, distributors, buyers, and other stakeholders can collaborate on the same platform thanks to the distributed ledger structure of the blockchain, which provides a secure, interoperable IT system (Jochumsen and Chaudhuri, 2018). In Europe, companies are required by the EU's Good Distribution Practice of Medicinal Products for Human Use (GDP 2013/C 343/01) to notify both the distributor and the recipient of the affected medicines of any changes in temperature or other conditions. By analyzing logistics data on transportation and duration, blockchain enables stakeholders in a supply chain to determine the accurate location and condition of the product (Kshetri, 2018). Further, to identify Adverse Drug Reactions (ADRs) quickly and accurately and effectively mitigate them, robust pharmacovigilance measures should be in place to provide clear and accurate product traceability by identifying the specific product, manufacturer, and batches (Felix et al., 2019). The management and resolution of crises, such as in the case of product recalls due to security flaws, can be facilitated by blockchain (Kshetri, 2017).

As with any emerging technology, the literature review also underscores the challenges that blockchain is facing. In a pharmaceutical supply chain as drugs travel through a network of distribution channels with multiple stakeholders and are not limited to a manufacturer, a wholesaler, or a retailer (Sylim et al., 2018), implementing blockchain requires bringing all relevant parties together, which can be challenging in many instances as the terms of a transaction or contract must be agreed upon by all participants (Kshetri, 2018; Alharthi et al., 2020). Another issue with implementing blockchain will be the handling of the data. The pharmaceutical industry generates significant data, and it will continue to grow. The result, apart from high storage costs, may lead to a decrease in the speed at which blockchains are distributed across the network (Alharthi et al., 2020). Finally, authorities must encourage and incentivize participants in the drug supply chains to make investments in infrastructure and human capital by proposing favorable policies (Sylim et al., 2018) as many, especially in developing countries, might be reluctant to adopt new technologies.

7 CONCLUSIONS

The pharmaceutical industry's profitability has garnered significant attention, yet it confronts challenges from counterfeiters who exploit vulnerabilities exacerbated by globalization and complex supply chains. In 2019, European authorities introduced Regulation EU 2016/161 to bolster drug supply chain security and traceability. By conducting a systematic literature review, this study evaluates the effectiveness of the European Drug Serialization system, analyzing its implementation and the potential advantages of

incorporating digital technologies like RFID and Blockchain. The primary objective is to fortify pharmaceutical supply chains against counterfeiting. The findings of the literature review show the importance of serialization while recognizing that it may not provide foolproof security, highlighting the necessity for additional integration of digital technologies.

As technology progresses, so do the associated challenges. The pharmaceutical industry's susceptibility to counterfeiting and criminal activities is heightened by its global reach and substantial economic interests. Governments and organizations worldwide have consistently strived to safeguard the pharmaceutical industry and protect human lives. Recent global data on counterfeit incidents involving pharmaceuticals indicate a troubling 38% increase from 2020 to 2021, with the highest number of incidents recorded in North America. Experts continually explore innovative and efficient technologies to create safer systems, with some advocating for combining RFID and barcodes, while others endorse more advanced solutions like blockchain to fortify their internal supply chains. Though the European authorities are currently relying on serialization efforts, a positive step toward securing the pharmaceutical supply chain, our findings of the literature review showed that the impact of future technologies on pharmaceutical drug security undoubtedly promises a favorable outlook. When effectively implemented alongside advanced technologies, pharmaceutical product serialization has the potential to serve as a valuable tool in safeguarding the supply chain from counterfeiting.

A key challenge for the pharmaceutical industry in implementing and integrating serialization or employing digital technologies in its complete supply chain operations lies in addressing the financial implications. Further research is recommended to explore newer technologies such as Artificial Intelligence and how financial concerns can be managed without compromising the security and traceability of pharmaceutical drugs.

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