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Review Article

Emerging Digital Technologies for Pharmaceutical Drug Traceability

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Abstract: The pharmaceutical supply chain environment has undergone tremendous change in recent decades due to technology, and this shift is intensifying. One of the main concerns of business practitioners is how to cost-effectively integrate, implement, and manage technologies across the supply chain of an organization. Pharmaceutical organizations that produce, ship, and supply goods have trouble tracking their goods, which makes it easier for counterfeiters to get fake medications into the system. The creation and implementation of a stringent technological system might be a significant step in the arduous battle against the prevalence of fake medications and other healthcare items. In supply chain management, digital technologies have a number of potential advantages. The usage of the Internet of Things in supply chains can make every component visible and create a visible supply chain, making it possible to identify the position and specifications of all the components and materials in the supply chain at any given time.

Keywords: Pharmaceutical Supply Chain, Drug Traceability, Drug Counterfeit, Pharmaceutical Serialization, Track and Trace System, Enterprise System, Blockchain, IoT

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1. Introduction

'Fake' medications pose a threat to patient safety and public health that has troubled the world community for decades. The risks posed by counterfeit and subpar medications have been identified all along the world's drug supply chain, including in traditional pharmacies, hospitals, clinics, unofficial marketplaces, drug distributors and traders, and through online sales [1, 2, 3]. The impact of these "fake" medicines is enormous because they have a negative impact on patient safety and treatment outcomes, cause waste, diversion, fraud, and abuse in the financing of healthcare and access to medications, undermine consumer confidence in pharmaceutical brands, reduce economic output in impacted communities, and have been linked to documented patient deaths [4, 5, 6, 7]. From the standpoint of population health, ignoring the harmful effects of fake medications can seriously jeopardize development and the billions of dollars invested in development assistance for health, frequently provided through sizable international aid programs intended to ensure equitable, secure, and life-saving access to essential medications [8]. Nearly 1000 distinct medical items, including medications from all major therapeutic categories, both generic and branded/innovator drugs, have been reported as fake or substandard to the WHO alone, illustrative of the problem's broad reach [9]. Additionally, a study that examined data compiled by the Pharmaceutical Security Institute (a nonprofit, membership organization of pharmaceutical company security directors) from 2009 to 2011 discovered that there were over 1500 fake medicine incidents reported in the 'legitimate' supply chain (i.e., segments of the supply chain that are regulated and where patients should reasonably expect to receive an authentic product) across 69 different countries [10]. Additionally, there has been a significant increase in journal papers on the topic,

showing that researchers, funding organizations, and the larger healthcare community are paying more attention to it [11, 12]. Even if there are numerous global networks of pharmaceutical suppliers, not all markets have the same risk factors or weak points [13]. However, a smaller proportion of medications also travel through the largely unregulated "gray market," which is populated by secondary wholesalers, traders, and resellers. [14] In this market, there is a significantly increased risk of finding medications that have been improperly stored, diverted, contaminated, counterfeit, or falsified [15]. Contrarily, numerous medication supply and distribution systems frequently operate in parallel within low- and lower middle-income nations, resulting in comparable variations in efficiency, quality, and oversight [16].

1.1. Online Counterfeit Medicine Market

Illegal and counterfeit pharmaceuticals are an international issue. The majority of fake pharmaceuticals are sold in developing or underdeveloped nations like South Asia and Africa, where the percentage might reach 70%. A third of the nations in the world don't have efficient regulating bodies for drugs, making them targets for counterfeiters. Millions of individuals are exposed to potentially deadly substances in the absence of anti-counterfeiting procedures, which also jeopardizes business expansion plans [17, 18]. The expansion of e-commerce platforms and the globalization of consumer markets have opened up new avenues for the distribution of fraudulent medications, including online shopping and delivery [19, 20]. Particularly, the availability, anonymity, affordability, and global reach of Internet-based technologies have facilitated the rapid proliferation of online pharmacies (estimated at over 35,000 websites), or more simply, websites that claim to operate as legitimate pharmacies via the Internet or mail-order and sell prescription drugs directly to consumers. But the vast majority of these online "pharmacies" operate unlawfully and without the necessary protections, such as not requiring a legitimate prescription, doing business without a legitimate license or certification, or failing to adhere to local, national, or international pharmacy rules [21, 22, 23]. These illegal or "rogue" online pharmacies pose a significant risk to patient safety because they serve as a source and point of distribution for medications of dubious quality, are not covered by the regulatory safeguards of the controlled supply chain, and lack clinical oversight from a clinician/physician, pharmacist, or other qualified healthcare professional [24]. Customers who buy prescription drugs from unlicensed online pharmacies actively help to undermine the regulatory framework intended to ensure the quality, safety, and proper use of these medications [25]. They also help to expand the market for the production, distribution, and dissemination of fake pharmaceuticals on a global scale. Cybersecurity dangers for consumers include financial theft, data phishing, and infection by computer viruses, malware, and spyware, which can exacerbate already-existing health-related damages. Therefore, the globalization of e-commerce has made it possible to establish a "digital" pharmaceutical gray market that is entirely independent from the legal supply chain, but in many ways more convenient but also just as risky. Importantly, continued difficulties with assuring fair access and affordability to prescription pharmaceuticals continue to be the key forces behind the continuation of this alternate demand and sourcing channel [26].

2. Digital Drug traceability in the supply chain

Drug serialization for digital traceability is required due to numerous instances of suspected or counterfeit medications in the pharmaceutical industry, which pose a major hazard to public health. The control of serialization has shown to be quite effective in preventing the sale of counterfeit medications [27]. Different strategies for safeguarding the integrity of the global drug supply chain are required to handle the particular difficulties brought on by various worldwide markets, supply chain dynamics, and legal jurisdictions, as physical and digital vulnerabilities continue to be uncovered. Authentication (i.e., scanning a medicine product at the point of supply through to the patient to verify

authenticity), serialization (i.e., identifying a medicine by using unique printed codes, images, or holograms on packaging to verify authenticity), and track and trace technology (i.e., logistic technology that tracks the present and previous locations of medical products through the supply chain) have been the main countermeasures for fake medicines [28, 29, 30, 31]. The security for electronic transactions and supply networks of other businesses (such as in the financial technology and e-commerce sectors) is changing despite the fact that these solutions have the potential to be effective. The global pharmaceutical supply chain is being used more and more to improve performance, management, and interoperability (including through the use of IT infrastructures, data analytics, inventory management, and end-to-end supply chains), but these same newly emerging "digital" technologies have not yet been fully tapped into to detect and prevent fake medicines. The potential use and translation of these solutions to solve the difficult drug safety dilemma of fake medications is still in its early stages, despite advancements in many digital technologies. Despite the fact that 3.5 billion people are now online and 95% of the world is connected to a mobile cellular network, the need for a digital "modernization" of the medication supply chain is developing. The DSCSA began its journey toward drug traceability in 2013 and has been steadily implementing compliance for more than eight years at this point. The implementation of the DSCSA 2023 Act is the biggest reform for the pharmaceutical business [32]. It will alter each phase of our business process. Importantly, by addressing supply chain weaknesses, these technologies may hold significant promise for reversing the tide in the fight against the trafficking in fake pharmaceuticals. However, a more thorough analysis is required to uncover opportunities and obstacles to their realization.

2.1. Mobile Technologies

Few technologies are as widely used as mobile phones, which currently have about 3.6 billion global mobile-cellular subscribers. Wireless or mobile-driven solutions to protect customers against fake pharmaceuticals appeared to be among the most mature given the pervasiveness of mobile phones in both developed and developing economies. These solutions are also particularly promising given their potential for scalability and user acceptance [33]. These solutions primarily aim to use mobile technology as a complementary approach to existing anticounterfeiting technologies by leveraging the expanding capabilities of mobile phone device platforms, software, built-in sensors, cameras, and ability to connect to GPS, wireless networks, and the Internet. Six significant commercial solutions that take a variety of approaches to the issue but all share a mobile platform as the underlying technology have been found as a result of our analysis of mobile technologies. These mobile technologies include tools for pill image identification, track and trace services, and authentication services. The introduction of many of these technologies over the past ten years has coincided with the growth and development of mobile features, from the 2005 debut of mPedigree to the more recent market arrival of Authenticate it in 2016.

2.2. Tamper-evident/ tamper-resistant packing

Packaging with an indicator or barrier to entrance that, if broken or absent, should alert customers visually or audibly that tampering has happened. Holograms are a highly effective tool against counterfeiting because they can combine three layered security elements. In such systems, covert elements like scrambled pictures, microtext, UV-sensitive or other specialized inks give second line authentication for qualified examiners and the necessary decoding tools, while overt features like holograms can provide overt first line authentication. Another development that combines authentication with traceability is the serialization of holograms [34]. Binary encrypted holograms, light-diffraction hologram components in product labels, or a fusion of a holographic, 2D datamatrix, and temperature monitoring are a few of these newly created technologies [35, 36]. Mandates for pharmaceutical serialization are gradually taking over the world. Serialization implementation

presents a number of unique difficulties, including noncompliant or useless bar codes, the potential for lost productivity on production lines, the requirement for significant human and financial resources for new procedures and data management, and inventory problems brought on by the improper tracking of returned goods. Drug packaging has been significantly impacted by serialization compliance, including label redesign and incorporation of serialization features, graphic components, and barcodes. Correct barcodes must be applied by the industry to pharmaceutical packaging in order to prevent confusion while evaluating potential questionable products [37, 38, 39].

2.3. Analytical Techniques

The supply chain can be verified by authentication using various anti-counterfeit technologies, and the content can be verified through analytical techniques like chromatography, optical spectroscopy, and isotopic characterisation [40]. Different pharmaceutical firms used a variety of analytical techniques to find fake medications. Simple methods like colorimetry and thin-layer chromatography are among them, as are more complex ones like NMR, mass, and raman spectroscopies [41]. The importance of handheld gadgets is currently increasing, and many new instruments are being created. Due of their non-destructive, quick, and dependable qualities, portable instruments like handheld raman and IR spectrometers are primarily used. Health authorities, regulators, and law enforcement organizations, in addition to pharmaceutical firms, have noticed an upsurge in demand for these. Some of the factors contributing to this demand include the fact that these are quick, unbreakable, portable, and simple for beginners to operate. There are further portable gadgets available, such as X-ray and mid IR spectrometers.

3. Digital Drug traceability using blockchain technology

Blockchain-related SC traceability research has drawn a lot of interest in recent years, and it's safe to say that this technology is now the most promising one for offering traceability-related services in supply chain networks. Data is validated through a distributed consensus process among a number of parties (devices/users connected to the network) in a decentralized manner thanks to blockchain technology [42]. Blockchain is a part of a larger class of technologies for distributed ledgers that may store transactions in a structured way. The outcomes of operations that take place between network nodes are represented by transactions. The idea of a blockchain as an immutable data structure is created by each block maintaining a reference to the preceding block through a cryptographic protocol. Although the blockchain guarantees that data and records on the network cannot be changed, there are still issues with product traceability, reliability, and the legitimacy of the parties involved. A trustworthy system is required to ensure traceability, trust, and delivery methods, particularly in situations like the supply chain of perishable goods and medications. The blockchain can be made more dependable by using smart contracts. In order to ensure careful monitoring of the transportation and distribution process in the supply chains for drugs, perishable goods, and agriculture, the Internet of Things can be used to track the conditions of the transportation process online and process the data that is intelligently collected from the sensors and stored in the blockchain. There are several platforms available to implement blockchain, including HyperLedger, Kaleido Blockchain Business Cloud, Salesforce Platform, IBM Blockchain Platform, and Azure Blockchain Workbench. We will favor Hyperledger over other platforms in this case. In order to create a collection of reliable frameworks, tools, and libraries for company-wide blockchain deployments, Hyperledger is an open-source project. From the start of the project process until stable code, Hyperledger hosts the development of blockchain applications using a modular manner. One of its primary objectives is to advance the distributed ledger and smart contract project [43]. The overwhelming amount of created data is one of the problems with blockchain-based systems. This issue appears when the system scales up, as in the case of IoT-based systems where a lot of data is generated over time,

or when the system data contains multimedia data. If all of the data were to be kept in the blockchain, there would be a tremendous need for storage space and bandwidth to synchronize the data with the network, which might discourage many nodes from joining the network [44]. Additionally, using such a database will take time. Utilizing the Interplanetary File System is one of the suggested fixes in such a system. Many nodes are presently running on the Ethereum mainnet using Hyperledger Besu, an open-source Ethereum client built on Java [45]. It utilizes the Ethereum mainnet as well as testnets like Rinkeby, Ropsten, Goerli, and Merge testnet as well as private networks. On both the Ethereum Mainnet and the Merge testnet, Besu serves as an executive client [46].

4. Conclusion

The pharmaceutical industry's need to identify and keep an eye on medications as they are distributed is examined in this study. The importance of this subject is stressed, especially in light of efforts to stop the sale of bogus pharmaceuticals. Decentralized medication handling using blockchain technology was developed and tested. The suggested approach uses smart contracts on the Hyperledger blockchain to automatically record events that can be seen by all participants and uses the cryptographic features of blockchain technology to ensure that information cannot be changed. A medication tracking system that incorporates IPFS and Hyperledger Besu will guarantee the supply chain's transparency and authenticity. Sensitive data is protected by the mix of a private and public state in Hyperledger Besu, while IPFS offers a productive off-chain data storage system.

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