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Global drug serialization in pharma sector: Complete review

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Abstract

The primary aim of this paper is to acquire an understanding of drug serialization within the pharmaceutical sector and explore its various dimensions. Presently, pharmaceutical counterfeiting poses a significant challenge in the industry. Various countries have established regulatory measures to combat counterfeit drugs, with drug serialization being one such regulatory compliance mechanism to address this issue. Over an extended period, counterfeit drugs have severely impacted the healthcare industry. Regulatory bodies across different nations are actively deliberating ways to alleviate the problem of counterfeit drugs and their adverse effects on consumers who unknowingly ingest fraudulent medications. Research indicates that in underdeveloped countries, as many as 4 out of 10 drugs are fake or have been adulterated through illicit means, contributing to a substantial problem. This situation has dire consequences for the healthcare industry, resulting in substantial financial losses due to the infiltration of counterfeit drugs into the supply chain. Additionally, consumers are put at risk when they unwittingly consume fake medicines, instead of the life-saving drugs they require. Regulatory authorities are responding by enacting new regulations to tackle this issue and prevent counterfeit or adulterated drugs from entering the supply chain. To ensure the safe and genuine delivery of drugs to patients, the pharmaceutical industry must implement robust traceability measures and adhere to stringent regulations. The tracking and tracing process of pharmaceutical drug serialization ensures the ability to trace individual drug packaging throughout the entire supply chain, encompassing manufacturers, distributors, wholesalers, pharmacies, and end consumers. Importantly, these serialization measures enhance the security of drugs within the supply chain without compromising drug quality, effectively reducing the infiltration of counterfeit drugs into the distribution network.

Keywords: Drug Traceability; Drug Counterfeit; Pharmaceutical Serialization; Supply chain; Track and Trace System; Cold Chain; Blockchain; Enterprise System

1. Introduction

Through the adoption of digital transformations, pharmaceutical organizations are revolutionizing their operational methods, incorporating innovative technologies into every facet of drug manufacturing and distribution. In order to ensure the distribution of genuine and secure pharmaceuticals within the supply chain, the implementation of drug serialization has become a crucial and stringent procedure. Often, counterfeit and adulterated medicines manufactured by illicit or unverified sources are deliberately mislabelled to obscure their authenticity and surreptitiously introduced into the supply chain for distribution. In the present day, pharmaceutical companies are making substantial investments in the development and implementation of digital technologies, aligning with regulatory requirements specific to their respective countries, with the primary objective of addressing the counterfeit drug issue within the supply chain. Illicit sources and networks, often facilitated through online channels, enable authorized counterfeit drug manufacturers to produce adulterated and fraudulent drugs, surreptitiously injecting them into the pharmaceutical supply chain.

The era of COVID-19 has exacerbated the challenges, with medication shortages, supply chain distribution complexities, reduced drug production, and heightened demand across various drug categories, all contributing to an increased risk

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of a surge in counterfeit drug production [1]. Drug supply chain's main stake holder manufacturer, Packager, primary and secondary wholesale distributors, dispenser, pharmacy, and ultimately patient and customers [2]. Typically, counterfeit drugs are illicitly peddled on the underground market, often beyond the borders of the manufacturing country, making it challenging for distributors to ascertain the authenticity of these medications. Such challenges are particularly prevalent in certain underdeveloped regions of Asia and Africa [3]. According to a report from the Alliance for Safe Online Pharmacies, approximately 50,000 online pharmacies, constituting 96% of them, fail to adhere to the regulatory standards established by authorities for patient safety and protection [4].

1.1. Benefit of the Serialization regulation

Counterfeit drugs lack the proper or adequate active ingredients, which can potentially result in harmful consequences for the patient. Alterations in the formulation of the drug may lead to life-threatening effects on the patient's health. Medications manufactured with fraudulent and adulterated active components can have enduring repercussions on a patient's well-being. As an example, in 2012, the consumption of counterfeit drugs led to the unfortunate deaths of more than 100 heart patients who were under treatment at the Punjab Institute of Cardiology in Pakistan [5]. Compliance with regulatory requirements stands as a significant concern for all pharmaceutical companies. These regulations have a direct impact on the reputation and trust of the brand among consumers [6]. In 2015, the FDA confiscated a stock of 18 million Lipitor tablets during various raids. These tablets had been brought into the United States through illicit channels, smuggled in from South American countries, and subsequently relabeled. A similar incident occurred in 2007-08 with the blood-thinning medication Heparin, resulting in the tragic deaths of approximately 149 patients due to counterfeit Heparin. Subsequent FDA investigations unveiled that the Heparin had entered the United States through illicit means. In 2003, the World Health Organization (WHO) estimated that illegal imports of counterfeit drugs by criminals and counterfeiters were generating an annual revenue exceeding \$32 billion [7]. These illicit proceeds significantly impact healthcare revenues and the capacity to invest in further research aimed at improving patient lives. The presence of opioid medications, classified as controlled substances, in the black market has resulted in numerous overdose-related deaths, causing substantial concern among regulatory agencies. In addition to these challenges, both GSK and Roche pharmaceutical organizations suffered revenue losses exceeding eight million dollars due to the infiltration of counterfeit drugs into the supply chain. A study from 2011 exposed a startling statistic: 64% of antimalarial medicines imported into Nigeria were potentially counterfeit. India and China, responsible for 70% of the imported drugs, are regarded as the primary sources of counterfeit medications [8]. The majority of counterfeit drugs globally originate from India, comprising 7%, while Egypt contributes 7%, and China accounts for 6% [9].

1.2. Globally Drug Serialization and Traceability Compliance

Worldwide, regulatory agencies in various countries are intensifying their efforts to enforce strict regulations regarding Drug Serialization and Traceability Compliance. The global healthcare sector is reaping the rewards of technological advancements and the expanded reach of pharmaceutical trade on a global scale. As a result, patients now have the option to purchase essential medications online from reliable sources, affording them greater accessibility to critical treatments [10]. Let's now delve into an examination of Drug Serialization and Traceability Compliance in key countries and regions.

1.3. Indian Regulations for Counterfeit Medicines

The Director General of Foreign Trade (DGFT) has introduced a mandate requiring all drug manufacturers to implement a three-tier serialization for their saleable units, categorizing them as Primary, Secondary, and Tertiary levels. As per this directive, export drugs must incorporate GS1 barcodes on their labels [11]. This legislation was enacted to address the challenges posed by counterfeit drugs and their impact on the pharmaceutical market. It serves to prevent many product recalls and also aligns with global standards, enabling the Indian pharmaceutical sector to maintain competitiveness in the international drug market. Since this law is harmonized with global regulations, data exchange with partner entities presents no significant hurdles and proceeds smoothly [12]. To comply with this legislation, drug formulations must bear a 2D barcode containing a 14-digit Global Trade Item Number (GTIN), batch number, expiration date, and a unique serial number. Export of drugs is contingent on both tertiary and secondary packaging carrying the requisite barcoding, and the associated data is uploaded to DAVA. Verification occurs at each packaging level in accordance with DAVA reporting guidelines [13]. Nevertheless, due to limited awareness about this law, manufacturers and packagers in the Indian pharmaceutical industry continue to grapple with issues related to product labelling and information. Instances of errors on barcode printing have been observed on homogeneous cases, including the use of multiple GTINs, the application of SSCC on homogenous packaging, the presence of multiple GTINs on the same case, and the use of the same GTIN on multiple aggregations of packaging.

1.4. United States Food and Drug Administration Regulations for Counterfeit Medicines

In Year 2013, US federal law Drug Quality and Security Act (DQSA), was enacted by Congress. DQSA bill required to solve the challenges about the drug quality and safety. DQSA bill had 2 titles to address specific requirement specifically. Compounding Quality Act, Title 1, and DSCSA, Title 2. DSCSA Tile 2 of the bill specifically address of the tracking system at unit level with framework for next 10 years [14].

Title II of the DQSA, or the Drug Supply Chain Security Act (DSCSA), enforce following guidelines on the partners in the supply chain of the pharmaceuticals drug.

- To implement the unique product code with the 2D Data Matrix on each sales unit for electronically traceability.
- To make sure all the distribution partners should have their identification as GLN.
- To ensure data transmission completed before transferring the ownership of the product.
- To ensure that all the distribution partner transfer data about the serialization information electronically for the unit level traceability.
- To check the return good before including it in the distribution supply chain again.

The DSCSA has established a 10-year timeline during which it plans to integrate blockchain technology into the traceability of pharmaceutical drugs [15,16]. Section 582(a)(9) of the FD&C Act, part of the Drug Supply Chain Security Act (DSCSA), mandates that each sales unit and its grouped similar packaging unit must feature a 2D matrix barcode that includes human-readable data [17]. Logistics traceability comprises three key components: tracking, tracing, and logging [18]. The 2D barcode is required to include essential information, such as the Global Trade Item Number (GTIN), expiration date, batch number, and a unique serial number. This same information should also be presented in human-readable form. All participants in the distribution supply chain, including manufacturers, distributors, wholesalers, repackagers, and dispensers, are obligated to electronically transmit serialized data to the next link in the chain prior to shipping the drugs. The DSCSA ensures that partners must electronically transfer aggregated data information to their supply chain counterparts. This data transfer is achieved through the exchange of EPCIS files [19]. Once again, tracking, tracing, and logging are the three fundamental components of logistics traceability [20].

1.5. European Union Guidelines for Counterfeit Medicines

The European Union's (EU) comprehensive regulatory framework for the authorization, production, and distribution of medications, which ensures that only authorized pharmacies can sell drugs, is primarily anchored in the Directive (2011/62/EU) concerning counterfeit medicines for human use. Authorized vendors are exclusively authorized to dispense pharmaceuticals, including legitimate online sales. The European Medicines Agency (EMA) and its collaborators play a pivotal role in closely overseeing the implementation of this legislation [21,22,23]. Counterfeiters frequently target drugs such as steroids, antihistamines, and hormones to infiltrate fake products into the supply chain. This includes expensive medications like anticancer drugs and high-demand drugs such as antivirals. In July 2011, EU regulators sought to enhance patient and consumer safety by enacting the Falsified Medicines Directive (2011/62/EU) concerning counterfeit pharmaceuticals for human use. This Directive officially came into effect on July 21, 2011, and by January 2013, Member States were required to commence the enforcement of their respective laws [24,25,26].

The European Union has implemented serialization legislation to encompass all prescribed medicines while excluding other pharmaceutical products. It is estimated that in European countries, approximately 10 billion packages of prescription medicines are dispensed by pharmacies falling under the purview of this serialization legislation [27]. According to this regulation, the Marketing Authorization Holder (MAH) is responsible for transmitting unit-level unique identifier data to a centralized cloud-based database, facilitating the traceability of medicines [28]. The European Medicines Verification System (EMVS) exhibits a distinctive structure that sets it apart. It establishes connections among approximately 2,000 pharmaceutical companies, around 6,000 wholesale distribution authorization holders, 140,000 pharmacies, 5,000 hospital pharmacies, and around 2,000 dispensing doctors across 28 EEA countries. As part of compliance, pharmaceutical manufacturers and parallel importers are now required to serialize the packaging of their prescription medicines with a Unique Identifier, embedded within a two-dimensional data matrix, and incorporate tamper verification features into the packaging. These Unique Identifiers are then uploaded by the manufacturers to the European Hub, known as the EMVS [29]. Manufacturers must communicate all serialization information about drug packages destined for the distribution supply chain to the central regulatory entity, the European Medicines Verification Organization (EMVO) before shipping (see Figure 1) [30].

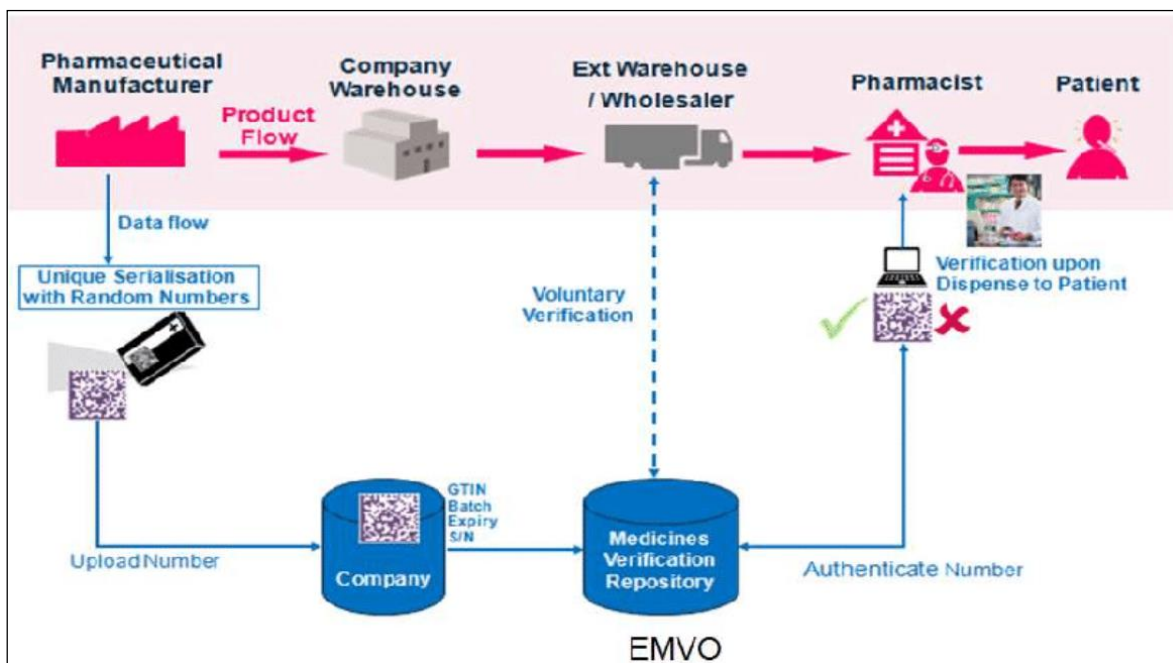


Figure 1 European Medicines Verification Organization (EMVO) Serialization and Traceability

1.6. Rest of the World – Serialization Compliance

Presently, regulatory agencies worldwide are universally embracing Drug Serialization compliance and integrating digital technologies to facilitate the traceability of serialization data. The International Council of Harmonization (ICH), established in 1990, is actively involved in fostering public health awareness by promoting the implementation of guidelines. In 2013, the World Health Organization initiated the Global Monitoring and Surveillance System (GSMS) to monitor and report instances of counterfeit medicines [31].

Regulatory authorities across the globe are diligently preparing to implement the track and trace procedures within their supply chains in accordance with their respective regulations. In China, every pharmaceutical product will be assigned a unique number by regulatory authorities and allocated to the manufacturer [32]. The Saudi Food and Drug Administration (SFDA) has made it mandatory that any prescribed medication produced or exported from Saudi Arabia must possess a unique identifier within each serialized prescription packet, adhering to the GS1 standard [33]. Turkey successfully instituted the Pharmaceutical Track and Trace System (PTTS) in 2013, which requires each product unit to be encoded with a distinctive 2D Data Matrix code as per regulations [34]. Furthermore, the Turkish Ministry of Health (MOH) has imposed regulations that necessitate serialization and tracking, encompassing unique serial numbers and 2D data matrix barcodes, for all product units, including bundles, shipper boxes, and pallets reimbursed by the government. These regulations extend to promotional samples, hospital-packaged items, prescription drugs, and over-the-counter medications [35]. Certain countries such as China and South Korea have already established serialization traceability regulations. Furthermore, the National Health Regulatory Authority in Bahrain has mandated specific information that must be present on individual pharmaceutical drug packages.

2. Conclusion

Pharmaceutical organizations continue to grapple with substantial challenges related to counterfeit drugs, leading to significant financial losses and putting patient lives at risk. The implementation of comprehensive drug track and trace and serialization regulations is a proactive response to combat this issue in the contemporary world. Moreover, the exchange of knowledge and information pertaining to serialization processes strengthens these controls. India and other developing nations are formulating their own rules to curtail the production of counterfeit medicines and their introduction into the drug supply chain. Developed countries such as the USA and Europe have already enacted stringent regulations to prevent the inflow of counterfeit drugs into their markets. Globally, nations are well-informed about the benefits of drug serialization in thwarting counterfeit drugs within the supply chain. By taking these measures, pharmaceutical organizations can reduce expenses, boost revenue, and enhance public health. Although the initial phases of serialization implementation may pose complexities and costs, the long-term advantages become evident as digitalization reduces data-sharing expenses and mitigates the revenue losses caused by counterfeit drugs.

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