

Pharmaceutical Drug Serialization: A Comprehensive Review

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Abstract: A persistent problem in the pharmaceutical industry that has existed for centuries is the prevalence of counterfeit drugs, and the World Health Organization (WHO) estimates that millions of people are affected by this issue each year. In particular, 4 out of 10 drugs in poor or underdeveloped countries may be adulterated, which can lead to severe adverse events. To address this problem, many countries have implemented regulatory compliance measures such as pharmaceutical drug serialization, which requires the unique identification of every drug package manufactured. This enables tracking and tracing of individual packages throughout the supply chain and helps to prevent counterfeit drugs from entering the market. In this paper, we conduct a systematic review of the serialization process evaluation and its impact on the pharmaceutical industry. We discuss the benefits of pharmaceutical drug serialization, including its ability to improve drug security and reduce adverse events and investigations. We also examine the challenges associated with implementing serialization processes and the regulatory requirements necessary for compliance. Finally, we explore the various tracking and tracing technologies used in serialization processes and their effectiveness in preventing the distribution of counterfeit drugs. Overall, this paper highlights the importance of pharmaceutical drug serialization in ensuring the safety and efficacy of drugs in the healthcare industry, particularly in poor or underdeveloped countries where the problem of adulterated drugs is especially prevalent.

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1. Introduction

Counterfeit drugs are pharmaceutical medicines that are intentionally manufactured and fraudulently labeled to conceal their true identity. This poses a significant risk to public health and has been a persistent problem in the pharmaceutical industry for many years. To combat this issue, pharmaceutical drug serialization has emerged as a crucial procedural concept to secure and authenticate drugs in the supply chain. As digital supply chain transformation continues to advance, traditional business practices are being replaced with more stringent technologies and regulatory compliance measures [1]. In the current pandemic era, the production and distribution of counterfeit drugs have increased due to the interruption of supply chains, non-business resilience, and the threat of ransomware. Criminals and drug counterfeiters have manufactured and supplied mass quantities of adulterated drugs through their illegal networks and online dark social platforms. The impact of counterfeit drugs on public health and the pharmaceutical industry cannot be overstated [2]. As such, the development and implementation of effective serialization processes are crucial for preventing the distribution of counterfeit drugs and ensuring patient safety.

1.1. The Evolutionary Drive for Serialization in Historical Context

Counterfeit drugs are a significant problem in the pharmaceutical industry. Such drugs may not contain the active ingredients required to treat the targeted disease, may

have hazardous substances, or may be mislabeled with incorrect information. A 2003 report by the World Health Organization estimated that counterfeiters and criminals earned over \$32 billion annually from counterfeit or substandard drugs [3]. A survey by Outsourcing Pharma in 2012 found that 75% of counterfeit drugs distributed globally had some origins from India, 7% from Egypt, and 6% from China [4]. There have been numerous instances of counterfeit drugs causing harm, including the deaths of over 100 heart patients in Pakistan who were treated with counterfeit drugs in 2012, and the deaths of 149 people in the US from an adulterated blood thinner in 2007-2008 [5]. In 2015, the FDA recalled almost 18 million Lipitor tablets from the market, which were found to have been diverted and smuggled into the US from South American countries. Additionally, criminals have smuggled and diverted around \$8 million worth of stolen drugs from GSK and Roche into the supply chain. Counterfeit medicines are mainly produced in India and China, with an estimated 64% of imported antimalarial medicines in Nigeria considered potentially counterfeit [6]. Tramadol, a controlled substance, has become a significant concern for regulatory agencies due to its presence in the black market and reported overdose-related deaths [7].

2. Global Adaptability Regarding the Revolution of Serialization Compliance

2.1. US Serialization Compliance

In the United States, there is a significant portion of the population that may be at risk of encountering counterfeit or stolen medicines. This risk is particularly prevalent among individuals who are Hispanic, have limited education, live in poverty, lack citizenship, lack health insurance, and have to bear high out-of-pocket expenses for healthcare. Some individuals may also be purchasing counterfeit drugs from illegal sources on the dark web or social media platforms [8]. To address this issue, the United States implemented serialization compliance in November 2018. Although the enforcement of serialization regulations was initially planned for November 2017, it was postponed for a year due to unpreparedness among manufacturers, supply chain partners, and wholesalers. Under the serialization regulation, all prescribed pharmaceutical medicines are required to have a unique product identifier for traceability. The Drug Supply Chain Security Act (DSCSA) came up with a plan to implement serialization between 2015 and 2023 [9]. This plan mandates the use of a unique product code with 2D data matrix in individual medicine packets for electronic traceability. Supply chain partners, including manufacturers, re-packagers, wholesalers, and dispensers, are required to transfer data electronically for unit-level traceability. In addition, packaging hierarchy of aggregated data must be included in an EPCIS file and transferred to supply chain partners electronically [10]. The DSCSA also requires that stakeholders in the supply chain, including wholesalers, distributors, dispensers, and pharmacies, verify the unique identifier of any suspected or potentially counterfeit products requested by trading partners, regulatory agencies, or state agencies. By 2023, the DSCSA will replace the requirement for lot-level traceability with unit-level traceability. All stakeholders in the supply chain will be required to exchange serialized data electronically using interoperable technological methods [11]. This provision will help the pharmaceutical industry adopt and leverage a more resilient system. The electronic traceable system must be capable of storing and processing massive volumes of data for product traceability [12].

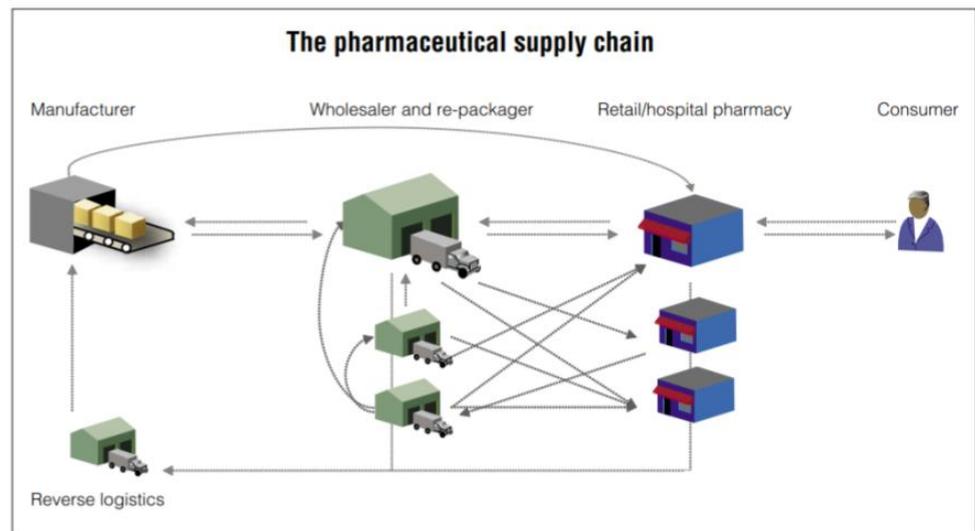


Figure 1. Pharmaceutical Supply chain

2.2. European Serialization Compliance

In 2011, the European Union Council introduced Directive 2011/62/EU, which aimed to mitigate the risks associated with counterfeit and stolen medicines in the European market. This directive amended the initial pharmaceutical legislative Directive 2001/83/EC, which later became the European Union Falsified Medicine Directive (EU-FMD). The legislative Delegated Regulation 2016/16 was crucial in enforcing serialization regulation in all European countries [13]. On February 9, 2019, the European Union enforced serialization legislative regulation, which only covers prescribed medicines instead of traceability provisions for all pharmaceutical drugs and devices. This regulation requires a centralized cloud-based product traceability system, which the Marketing Authorization Holder (MAH) uses to transfer unit-level unique identifier data to a centralized cloud-based database for further medicine traceability. The "Book-End" approach requires every stakeholder in the supply chain to verify the unique identifier encoded in product labels [14]. The European Union's drug traceability model emphasizes patient safety, data confidentiality, a resilient system, and reliability of transaction data throughout the supply chain. The European Medicines Verification Organization (EMVO) serves as a place to store data related to medicine traceability. It is connected with National Medicine Verification Systems (NMVS), which transfers data to NMVS database repositories. Each EU country must have its verification system that connects with EMVO for verification of unique product identifiers. NMVS systems connect with pharmacies/hospitals of that particular country and change the status of the unique identifier of medicine as decommissioned when it dispenses to the final consumer.

2.3. Other - Serialization Compliance

Currently, many regulatory agencies across the world are adopting serialization compliance and implementing track and trace systems for medicine traceability. The International Council of Harmonization (ICH), founded in 1990, promotes public health awareness through the implementation of guidelines. In 2013, the World Health Organization launched the Global Monitoring and Surveillance System (GSMS) to report and track counterfeit medicine. The implementation of serialization traceability processes in the supply chain is not a new concept, as Turkey successfully implemented the Pharmaceutical Track and Trace System (PTTS) back in 2013 [15, 16]. Some other countries, such as China and South Korea, have serialization traceability regulations in place [17].

For example, in China, all pharmaceutical drugs are required to have a unique number allocated to the manufacturer by the regulatory authority [18]. The Saudi Food and Drug Administration (SFDA) mandates that any prescribed medicine manufactured or exported in Saudi Arabia must have a unique identifier in each prescribed serialization packet, as per the GS1 standard [19]. Similarly, the National Health Regulatory Authority in Bahrain mandates that individual pharmaceutical drug packages must bear specific information.

- Global Trade Item Number (GTIN) (14-digit fixed length with application Identifier 01)
- Expiration Date in YY/MM/DD format with application identifier 17
- Serial Number up to 20 characters length with application identifier 21
- Batch or Lot Number with application identifier 10

For complete traceability, individual pharmaceutical drug packages in Bahrain must include a GTIN, unique serial number, batch and lot expiry information, and record every activity including commission, aggregation, and ship events. All products imported or manufactured in Bahrain must upload their unique serial number into the NHRA-MVC Traceability Hub, and all stakeholders in the supply chain, including wholesalers, distributors, dispensers, pharmacies, and hospitals, must verify the unique identifier during the dispensing process to the consumer [20].

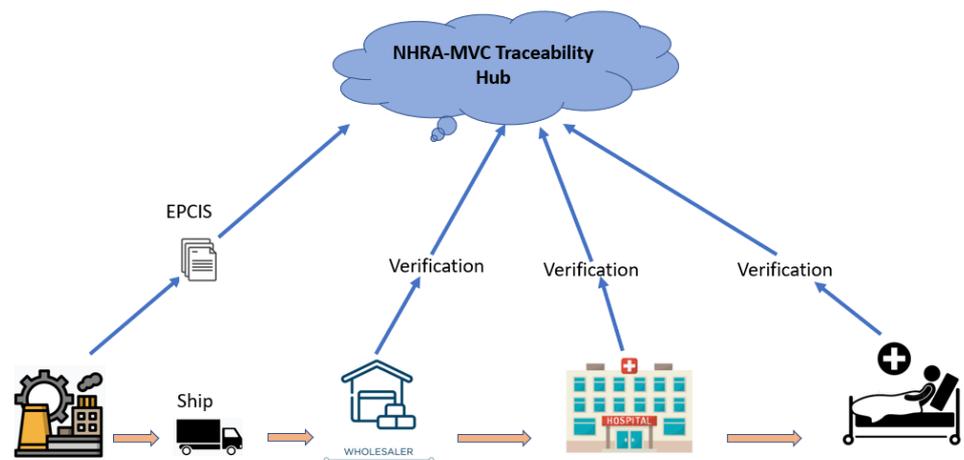


Figure 2. Bahrain traceability Hub

3. Serialization Barcode

Barcodes are essential in the pharmaceutical industry for tracking and tracing products to improve patient safety and combat counterfeit drugs. The HDA has updated its guidelines to ensure compliance with evolving product safety and patient healthcare systems. Serialization compliance became effective in the United States on November 27, 2023, making the use of barcoding requirements mandatory for unit labels, case labels, and pallet labels to encode unique identifiers for product traceability. The adoption of RFID barcode technologies, such as GS1-DataMatrix and GS1-Databar, is recommended due to their larger data capacity, cost-effectiveness, and compatibility with regulatory standards [21, 22]. Serialization implementation involves encoding a unique identifier, tamper-proof seals, and holograms in unit and case-level packages. The Drug Supply Chain Security Act (DSCSA) and HDA guidelines play a significant role in ensuring compliance and establishing an electronic, interoperable system for drug identification and traceability [23, 24, 25, 26]. Accurate and readable barcodes are crucial in mitigating

the risk of counterfeit drugs and ensuring proper medication administration to patients [27, 28]. The guidelines specify the inclusion of standardized numerical identifiers, lot numbers, expiration dates, and GTIN in the 2D DataMatrix barcode format. Adherence to FDA recommendations regarding the human-readable format of product identifiers, lot numbers, and expiration dates is essential. In conclusion, barcodes play a critical role in enhancing product security, traceability, and patient safety in the pharmaceutical supply chain [29].



Figure 3. 2D Datamatrix serialized barcode for unit level pack



Figure 4. 2D Datamatrix serialized barcode for Shipper case

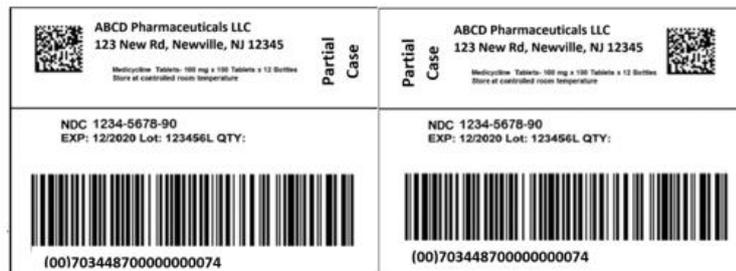


Figure 5. 1D Linear SSCC embaded barcode for pallet

4. Challenges and limitations of serialization implementation

Serialization implementation can pose significant challenges and limitations, particularly for small and developing countries. One of the primary challenges faced by small and developing countries is financial constraints. These countries often have limited

funds available for investing in the development and implementation of serialization systems. In addition to that, infrastructure limitations also pose a significant challenge because effective serialization implementation requires a robust and reliable infrastructure, including secure networks, data centers, and connectivity solutions. However, small and developing countries may lack the necessary infrastructure or suffer from inadequate coverage, hindering the seamless transmission and tracking of serialized data. This can impede the successful operation of serialization processes. Technological barriers further complicate serialization implementation in these regions [30, 31, 32, 33, 34, 35, 36].

Adopting serialization technologies often requires a certain level of technical expertise and knowledge. However, small and developing countries may face challenges due to the limited availability of skilled personnel and the need to train existing staff on serialization systems. Insufficient technical capabilities can hinder the implementation and operation of serialization processes, impeding progress in this area. Regulatory compliance is another significant challenge for small and developing countries. Serialization implementation is often driven by complex regulatory requirements, particularly in sectors like pharmaceuticals and healthcare. However, these countries may struggle to keep up with evolving regulations and guidelines related to serialization. They may lack dedicated regulatory bodies or comprehensive frameworks, making compliance efforts challenging and time-consuming [37].

Supply chain complexity adds another layer of difficulty. Small and developing countries often have fragmented supply chains with multiple intermediaries and limited visibility. Integrating serialization into such complex supply chains can be challenging and may require coordination among various stakeholders. Streamlining supply chain processes and enhancing collaboration among industry participants are crucial to overcoming these challenges. The counterfeit market poses a significant hurdle for serialization implementation in small and developing countries. These regions often face a higher risk of counterfeit products [38, 39, 40, 41, 42].

While serialization can help combat counterfeiting, it is not a standalone solution. Eradicating the counterfeit market requires a comprehensive approach, including robust enforcement mechanisms and regulatory capabilities. Implementing serialization systems alone may not be sufficient to completely eliminate counterfeit products in these countries. Data privacy and security are critical considerations in serialization implementation. However, small and developing countries may face challenges in implementing these measures and maintaining the necessary cybersecurity infrastructure. This might lead to potentially exposing them to unauthorized access and misuse of data. To address these challenges, small and developing countries can seek assistance from international organizations, collaborate with neighboring countries, and leverage partnerships with technology providers. Sharing resources, knowledge, and best practices can help mitigate the limitations of serialization implementation and ensure its successful adoption in these regions. By addressing these challenges proactively, small and developing countries can harness the benefits of serialization, enhance supply chain integrity, and safeguard their populations from counterfeit products [43, 44, 45, 46, 47].

5. Conclusion

This paper highlights the significance of pharmaceutical drug serialization in addressing the persistent issue of counterfeit drugs in the pharmaceutical industry. Counterfeit drugs pose a substantial risk to public health, with millions of people affected each year. Pharmaceutical drug serialization, which involves unique identification of every drug package manufactured, enables tracking and tracing throughout the supply chain, thereby preventing counterfeit drugs from entering the market. The paper emphasizes the benefits of serialization, including improved drug security, reduced adverse events, and enhanced investigation capabilities. However, implementing

serialization processes comes with challenges and regulatory requirements that must be addressed. Various tracking and tracing technologies are employed in serialization processes, with barcode technologies such as GS1-DataMatrix and GS1-Databar being recommended for their data capacity, cost-effectiveness, and regulatory compatibility. Accurate and readable barcodes are crucial in combating counterfeit drugs and ensuring patient safety. Overall, pharmaceutical drug serialization plays a crucial role in safeguarding the healthcare industry and particularly benefits underdeveloped countries where the problem of adulterated drugs is prevalent.

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