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Pharmaceutical sector: Packaging requirement in serialization

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Abstract

Access to healthcare is a fundamental right for every individual, and it is the responsibility of governments to ensure the provision of quality healthcare services and infrastructure to their citizens. Over the past few decades, both governments and the healthcare industry have been grappling with the challenge of minimizing the adverse effects on public health caused by counterfeit medicines. According to the World Health Organization, approximately four out of ten medicines in developing and impoverished countries are either fake or potentially adulterated, leading to significant economic losses and reducing funds allocated for research and development (R&D) by organizations. Preventing counterfeit medicines from entering the supply chain poses a significant challenge for governments and regulatory authorities. Consequently, there is a concerted effort to establish stringent guidelines aimed at thwarting criminals and counterfeiters from infiltrating markets with fake medications. The healthcare industry recognizes the necessity for strict regulations and secure technologies to ensure the provision of safe and authentic drugs to patients. In the United States, the FDA has outlined a ten-year roadmap to implement drug traceability measures. Additionally, the Healthcare Distribution Alliance (HDA) has mandated the inclusion of multiple barcodes and human-readable data in product packaging hierarchy. Furthermore, the FDA is actively engaged in a pilot project with leading pharmaceutical manufacturers and wholesalers to explore the utilization of blockchain technology within an interoperable digital network for securing the transfer of digital traceability data among authorized trading partners.

Keywords: Drug Traceability; Pharmaceutical Serialization; Track and Trace System; Healthcare supply chain; GS1 Barcode.

1. Introduction

Pharmaceutical drug serialization represents a pivotal approach to digitally track and trace drugs throughout the supply chain. The complexity of digital drug traceability in the supply chain is multifaceted [1]. It involves continuous changes in brand ownership of drugs between manufacturers and buyers. The absence of stringent regulations and secure technology within the supply chain poses threats to all stakeholders, including patient safety. Any errors or adverse events occurring in the manufacturing process, supply chain procedures, material sourcing, ideal storage conditions, or temperature maintenance can compromise the potency of drugs, thereby impacting people's health. The pharmaceutical industry consistently attracts criminals and drug traffickers who produce large quantities of counterfeit medicines and distribute them through illicit networks and online channels, including the dark web [2,3]. The COVID-19 pandemic has exacerbated this issue, leading to an increase in counterfeit drug production due to disruptions, a lack of skilled resources, low business resilience, and the rapid misuse of technology. Technology now influences virtually every facet of our behaviour and personal experiences. The commercial and economic landscape is constantly evolving as a result [4].

The adverse economic impacts experienced by the healthcare sector due to counterfeit and illicit drugs result in significant revenue losses for supply chain partners. This illicit trade diminishes the profitability of the health sector

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and reduces its capacity to invest in pharmaceutical research and innovation for economic growth. Several blockchain-based applications, coupled with advanced manufacturing technologies, are being employed to enhance digital drug traceability, marking continuous improvements at the forefront of innovation. Critical and desirable areas for systematic tracking and investigation include material traceability in continuous manufacturing systems [5]. Within the current competitive economic landscape of the pharmaceutical industry, traceability emerges as a key differentiator, facilitating waste reduction, counterfeit prevention, and minimizing targeted recalls to enhance supply chain processes. This approach aims to improve process synchronization, adaptability, visibility, resilience, and security.

Technologies play a crucial role in combating the process of counterfeiting drugs. In today's landscape, it has become increasingly easy to produce products that initially appear to be genuine. Additionally, the accessibility of the online drugs market, often referred to as the grey market, poses a significant threat. The rapid expansion of online pharmacies increases the risk to people's lives. Therefore, the serialization process has emerged as a universal tool and primary procedure in the fight against counterfeiting [6,7].

Pharmaceutical serialization has emerged as a pressing challenge aimed at enhancing the traceability of drugs. It has become an urgent necessity in the global endeavour to combat the sale of counterfeit medicines, which poses a growing and significant threat to patients' health. In contrast to conventional systems that depend on a central database, Blockchain disperses data across a network, thereby improving stability and minimizing vulnerability to hacking [8]. The overarching objective of this paper is to provide an overview of the current general aspects surrounding the implementation of the serialization process. Specifically, it aims to delineate the modern methods that have surfaced to enhance serialization, examine the existing legislative regulations, discuss the steps being taken towards global harmonization, and explore the active mechanisms of serialization in the fight against counterfeit medicines. The primary audience targeted includes healthcare professionals and specialists in the pharmaceutical industry. Nevertheless, there is considerable new territory to be explored in the realm of supply chain management and serialization/traceability [9].

2. Packaging used in the Pharmaceutical serialization

The majority of countries have already embraced pharmaceutical serialization regulations, ensuring compliance in drug manufacturing processes according to established standards. However, many manufacturers encounter challenges during implementation, such as non-compliance resulting from incompatible barcode formats. [10] This non-compliance and barcode incompatibility can lead to potential productivity losses on production lines, necessitating significant human and capital investments for new data management processes and inventory complications, thus increasing the risk of uncontrolled tracking of returned serialized medicine. The 2D barcodes for vaccinations, medical equipment, or medications can aid the responsible organizations by encouraging an effective inventory procedure and by providing crucial information for methods of global distribution [11].

The introduction of digital drug serialization regulations has significantly impacted drug packaging. This includes redesigning labels, realignments, and the incorporation of serialization product data, product graphic elements, and pharmaceutical barcodes in accordance with guidelines provided by the Healthcare Distribution Alliance (HDA) [12]. The packaging of pharmaceuticals differs depending on the specific drug; however, typically, there are three levels of packaging: primary packaging, secondary packaging, and tertiary packaging.

3. Primary Packaging

Pharmaceutical primary packaging constitutes the initial layer directly attached to a product. Upon unboxing pharmaceuticals, it serves as the final layer to be removed for product utilization. Its primary purpose is to maintain the product's optimal condition while ensuring user-friendliness and an appealing appearance. Given the dynamic nature of the pharmaceutical industry, packaging must evolve accordingly. Selecting the appropriate material for primary packaging entails a meticulous understanding of the drug's chemical composition and its compatibility with various materials. This necessitates manufacturers to strike a delicate balance between functionality and aesthetics [13]. Furthermore, the choice of material influences machinery selection, ranging from blister packaging machines to vial filling machines, depending on the primary packaging material chosen. This pertains to packaging materials that directly interact with pharmaceutical preparations. An illustration of this would be plastic blister packs with foil lids.

The primary packaging refers to the packaging that directly interfaces with the drug. Within the vial and bottle industry, the aluminum blister serves as the predominant form of primary packaging. Notably, the serialization of primary

packaging is mandated solely in the American and Indian markets. This requirement arises from the fact that in these markets, albeit uncommonly, patients have the opportunity to purchase primary packaging [14].

The Regulations mandates the inclusion of a unique serial number identifier on each product package and homogeneous case. In its final guidance, the FDA clarified that it is acceptable to include the National Drug Code (NDC) within the Global Trade Item Number (GTIN) in the machine-readable 2D barcode required by the DSCSA. Additionally, the NDC may be optionally presented in the human-readable portion of the product identifier. The product identifier is represented as a standardized graphic in both human-readable format and on a machine-readable data carrier, known as a 2D DataMatrix barcode [15]. The GS1 Data Matrix, a two-dimensional (2D) barcode, efficiently enables the encoding and marking of a larger amount of data within a smaller area. It also provides error detection and correction capabilities, enhancing barcode readability even in cases of irregular packaging or label damage [16]. According to GS1 guidelines, compliance with the DSCSA requires the inclusion of the GTIN Application Identifier (AI) (01), the serial number AI (21), the lot number AI (10), and the expiration date AI (17) to create the DSCSA-compliant product identifier encoded in a 2D Data Matrix barcode.

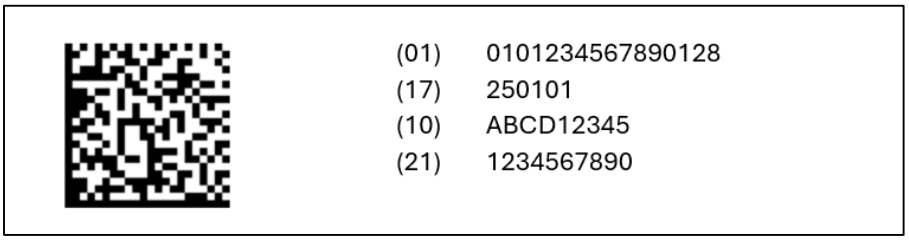

Figure 1 Data Matrix Barcode on the Primary Packaging

4. Secondary Packaging

Secondary packaging in pharmaceuticals encompasses the portion that envelops both the medication and the box containing the product. Its role extends to providing supplementary protection, enhancing convenience and usability, and serving as an informational platform for clients regarding the drug's composition, therapeutic indications, dosage regimen, potential side effects, and storage conditions. Furthermore, it serves as a medium for the product's branding, with colors, typography, logos, and other design elements contributing to brand recognition and market appeal. Thus, meticulous design of secondary packaging holds the potential to significantly augment product differentiation and foster brand loyalty in a fiercely competitive market. Examples of pharmaceutical secondary packaging include blister cards, blister wallets, and folding cartons, Shipper Case [17,18].

This refers to the packaging that encases the primary packaged medicine or medicines, with the carton being a prime example. Serialization of this packaging is essential for compliance with regulations. Certain regulations, like the EU-FMD, necessitate Tamper Evident features, in addition to pharmaceutical serialization, to ensure that the medicine is initially opened by the patient.

Figure 2 Serialized Label for the Secondary Packaging – Full Case

Figure 3 Serialized Label for the Secondary Packaging – Partial Case

5. Tertiary packaging

Finally, tertiary packaging in the pharmaceutical sector serves primarily for shipping and transportation needs. Frequently, this tertiary packaging remains unseen by end-users, as retailers typically remove it before sale. Common forms of tertiary packaging in the pharmaceutical industry include cardboard boxes, pallets, and shrink film. This packaging must possess sufficient durability to withstand environmental challenges during transit, such as temperature variations, humidity, and physical impacts [19,20]. Despite its lack of direct interaction with the product, its role in preserving the overall integrity of the product throughout the logistics process is of utmost importance. The serialization of tertiary packaging is the most important point to ensure traceability in the supply chain. Every enterprise engaged in shipping goods incorporates tertiary packaging within its distribution operations. Essentially, tertiary packaging serves the dual purpose of safeguarding both the product and the underlying packaging during transportation from one location to another.

At the top tier of packaging, this could consist of a shipper case or a palletized unit holding multiple shipper cases intended for separate transport. Each label is equipped with a 1D barcode containing a SSCC. Contained within this tier are homogeneous cases, which hold inner packs at the smallest sales unit (Primary or secondary), and heterogeneous cases, which accommodate various products. Below Picture shows the proof of SSCC Label for the tertiary packaging and its Barcode structure to understand it better.

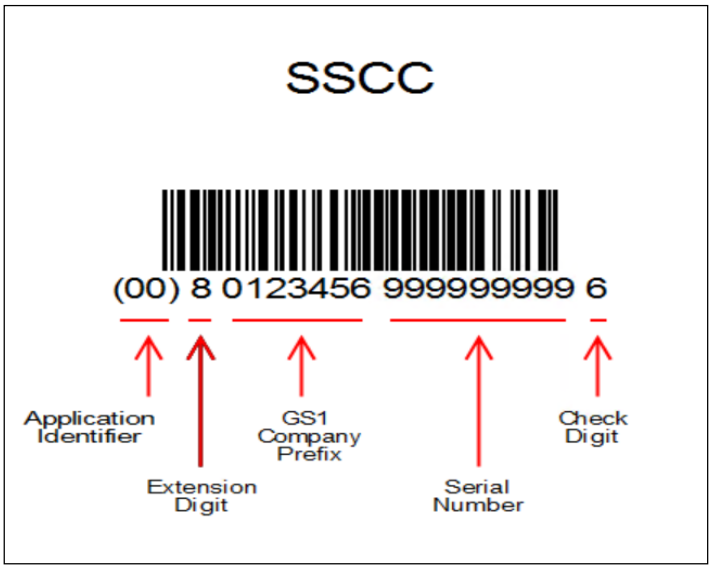

Figure 4 SSCC Barcode on Tertiary Packaging

6. Challenges in Pharmaceuticals serialization:

In practical terms, supply chain risk and uncertainty are often used interchangeably. Uncertainty and risk within the supply chain can manifest in various forms and originate from diverse sources, effects, and drivers. Internal operations uncertainty and risk may entail unforeseen incidents, outcomes, or accidents occurring during internal processes [21]. Additionally, these uncertainties provide opportunities for drug traffickers and counterfeiters to sell drugs on dark web platforms and social media channels [22].

Consumers are attracted to purchasing medicines online for several reasons, including geographical restrictions, lower prices, rapid time to market, direct customer targeting, and expanded customer reach. Another significant obstacle to the implementation of pharmaceutical serialization is the requirement for manufacturers or supply chain participants to generate, document, and disseminate serialized event data to clients and regulatory bodies. This necessitates sharing data over a restricted and secure network.

Regrettably, impoverished and developing nations encounter significant hurdles such as inadequate funding for infrastructure enhancements, a shortage of skilled personnel, the absence of secure technology, and the inability of local pharmaceutical manufacturers to embrace and invest in drug traceability systems. Small-scale manufacturers face critical challenges stemming from geopolitical and economic disparities, civil conflicts and political instability, a lack of trust in government entities, and the ramifications of climate change and environmental fragility [23, 24, 25]. The wholesalers and distributors should be in charge of using the cloud-based database hub to check the validity of medications all along the supply chain as part of the supply chain process [26].

The implementation and maintenance of a serialization system for drug traceability necessitate skilled resources. Any human, mechanical, or technical error can have adverse consequences for human life. In India, the Directorate General of Foreign Trade's (DGFT) requirement for manufacturers to upload "dummy" or counterfeit serial numbers for primary packaging (such as individual vials, blister cards, or bottles) that are not serialized is potentially one of the most perplexing stipulations [27].

7. Conclusion

Pharmaceutical packaging plays a vital role in ensuring drug security during serialization processes. The Drug Supply Chain Security Act (DSCSA) mandates manufacturers to incorporate a 2D Data Matrix symbology barcode and standardized case labels on their products to ensure international compliance with serialization requirements within the supply chain. Additionally, the DSCSA requires the printing of GS1-2D Data Matrix barcodes alongside human-readable formats, aligning with norms established by internationally recognized standards development organizations.

The encoded serialized data within the barcodes facilitates supply chain harmonization in global trade, enhancing the ease and reliability of data reading through radio frequency equipment. By providing a unique product identity, these barcodes mitigate the risk of counterfeiting. According to the DSCSA, a product's identifier must conform to a "standardized graphic" that includes the standardized numerical identifier, lot number, and expiration date, in both machine-readable and internationally recognized human-readable forms.

To further enhance product security along the supply chain, tamper-evident features should be incorporated into additional medicine packaging. The DSCSA mandates the electronic transmission of serialization data in an interoperable manner by manufacturers, wholesalers, and distributors, where barcodes on pharmaceutical supply chains play a pivotal role in mitigating the risk of medication counterfeiting.

Barcode labeling is crucial for reducing the risk of pharmaceutical errors and ensuring patient safety. Precise placement of barcodes on medication is essential to avoid errors that could lead to batch recalls, inquiries, confusion, and delays within the supply chain.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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