Systematic review of pharmaceutical drugs serialization

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Abstract:

The purpose of this paper is to review systematically serialization process evaluation. Generally, pharmaceutical drug serialization is a regulatory compliance adopted by major countries for fighting against pharmaceutical drugs counterfeiting. Since 19th century, the drug counterfeiting is major problem for healthcare industry. Periodically, the regulatory and healthcare agencies are struggling to mitigate the risk of adverse events caused by the counterfeit drugs. The World Health Organization (WHO) has estimated that 4 out of 10 drugs available in poor or under developing countries are potentially adulterated. Ultimately, the drug manufacturers are losing billions of dollars every year due to stolen, diverted and counterfeit drugs. Currently, the regulatory authorities are adopting the stringent guidelines to restrict criminals to supply and divert counterfeit/stolen medicine in the supply chain. Healthcare industry need rigorous regulations and secure traceability technologies to provide safe and genuine drugs to the patients. Basically, the pharmaceutical drug serialization reveals advantages by improving the drug security in supply chain by reducing adverse events and investigations. Further, pharmaceutical drug serialization is based on tracking and tracing technological capabilities which leverage the benefit of tracing individual drug package in supply chain.

Keywords: Drug Traceability, Pharmaceutical Serialization, Drug Counterfeit, Supply chain, Track and Trace System.

I. INTRODUCTION

Generally, Counterfeit drugs are pharmaceutical medicines intentionally and fraudulently manufactured and mislabelled to hide the authentication of drug. Furthermore, the pharmaceutical drugs serialization is a strong procedural concept to secure and authenticate pharmaceuticals drugs in the supply chain. At Present, digital supply change transformation is changing the scope of traditional business and leveraging the benefits of advances technologies. Finally, the pharmaceutical companies are adopting more stringent technologies and regulatory compliance to tackle the drug counterfeiting issues in the supply chain. In current Pandemic era, Criminals and drug counterfeiter manufactured mass quantities of adulterate drugs and supply them through

their source of illegal network and online dark social platforms. Furthermore, the mass production of counterfeit drugs has increased due to COVID-19 interruption in supply chain, non-business resilience and threat of ransomware [1]. Basically, to measure the exact size of counterfeit drug market, four potential scenarios are evaluated that are associated with an estimated global counterfeit drug market of $100 billion, $200 billion, $300 billion, and $431 billion, respectively. (Henry I. Miller & Waye Winegarden, 2020) [2]

II. HISTORICAL REASONS FOR PHARMACEUTICAL SERIALIZATION NEED

By Nature, Counterfeit drugs have no or less active ingredients, and somethings have substance of hazardous, adulterants, fake ingredients, completely mislabelled, or supply with a incorrect brand name. In 2003, the World Health Organization (WHO) has estimated that criminals and counterfeiters are earning over $32 billion annually from substandard and/or counterfeit drugs [3]. The Outsourcing Pharma conducted survey in 2012 and found that, 75% of counterfeit drugs distributed globally had some origins from India, 7% from Egypt and 6% from China [4]. In the 2012, over 100 heart patients died after treated with counterfeit drug by Punjab Institute of Cardiology in Pakistan [5]. In year 2007-08, around 149 people died from adulterated blood thinner called heparin. Further investigation by FDA revealed that Heparin was legally imported into United States. In 2015, FDA has recalled near about 18 million Lipitor tablets from market. After Investigation by agencies, it discovered that Lipitor and Celebrex were diverted and smuggled into United States from South American countries and relabelled to hide the true origin of medicine. Furthermore, criminals diverted about eight million dollars' worth of stolen GSK and Roche drugs into supply chain. In 2011, it was estimated around 64% antimalarial medicines imported into Nigeria were potentially counterfeited. India and China accounted 70% of imported drugs and considered main source of counterfeit medicines [6]. Later, Tramadol, a control substance medicine of opioid became biggest concern for regulatory agencies as it created huge black market and number of overdose related deaths were reported [7].

III. GLOBAL ADAPTABILITY OF SERIALIZATION COMPLIANCE

• US SERIALIZATION COMPLIANCE

In United States, Majority of population is potentially under the risk of exposing the counterfeit or stolen medicines. Generally, the population who are Hispanic, school educated, under poverty status, non-citizen, without health insurance, managing high cost out of pocket insurance expenses and purchasing counterfeit drugs from illegal dark web or social media platform [8]. Fundamentally, United States of America came into the serialization compliance on November 2018. However, it was announced to enforce serialization

regulation on November 2017 but due to non-readiness of the manufacturers, the supply chain partners and wholesaler, compliance delayed for one year. Under this serialization regulation, all prescribed pharmaceutical medicines need to have unique product identifier for traceability. Drug Supply Chain Security Act (DSCSA) has strategized an eight-year step by step implementation plan between 2015 to 2023. Under this strategy, it has regulated mandatory compliance for implementing unique product code with 2D data matrix in the individual medicine packets for electronic traceability. Further, all the supply chain partner including manufacturer, re-packagers, wholesaler and dispensers needs to transfer data electronically for unit level traceability. Moreover, it also requires to include packaging hierarchy of aggregated data in EPCIS file and transfer them to the supply chain partner electronically [9] The Drug Supply Chain Security Act (DSCSA) regulates that the stake holders in the supply chain including wholesaler, distributor, dispenser and pharmacy must to verify the suspected or potentially counterfeit product unique identifier requested by trading partner, regulatory or state agency [10]. Ultimately, the DSCSA 2023 Act also replace the lot level requirement to unit level traceability and all stake holders in supply chain must to exchange serialized data electronically in the interoperable technological method. Further, this provision will help pharmaceutical industries to adopt and leverage resilient system. The electronic traceable system should be capable enough to store and process mass volume of data for product traceability. The Drug Supply Chain Security Act (DSCSA) section 582(a)(9) of the FD&C Act., recommend that each product packaging must include a 2-dimensional (2D) data matrix barcode with human readable form of data when printing product packaging labels and in a linear barcode or 2D data matrix barcode when printing label on a homogenous case [11].

• EUROPEAN SERIALIZATION COMPLIACNE

European Union council has introduced legislative Directive 2011/62/EU in 2011 and initiated a plan to mitigate the risk of counterfeit and stolen medicine in European market. Basically, it amended the initial pharmaceutical legislative Directive 2001/83/EC later which became European Union Falsified Medicine Directive (EU-FMD). Furthermore, the legislative Delegated Regulation 2016/16 played a crucial role for enforcing serialization regulation in all European countries. Finally, on February 9, 2019, European Union has enforced serialization legislative regulation. Actually, this regulation only covers the prescribed medicine instead of traceability provision for all pharmaceutical drugs and devices. It is estimated that around 10 billion packages of prescription medicines are dispensed by pharmacies across European countries [12]. Under this regulation, a centralized cloud-based product traceability system was adopted. In this regulation, Marketing Authorization Holder (MAH) will transfer unit level unique identifier data to centralized cloud-based database

for further medicine traceability. European Union has adopted “Book-End” approach where every stakeholder in the supply chain must verify unique identifier encoded in product labels [13]. European Union drug traceability model leverage patient safety, data confidentiality, resilient system and reliability of transaction data throughout the supply chain. European medicines Verification Organization (EMVO) is central cloud-based data repository for medicine traceability. Further it connected with National Medicine Verification system (NMVS) and transfer data to NMVS database repository. As per European regulation, every EU country must have their verification system which should connect with EMVO for verification of unique product identifier. NMVS system connected with pharmacies/hospitals of that particular country and change the status of unique identifier of medicine as decommissioned when it dispenses to final consumer.

• SERIALIZATION COMPLIANCE - REST OF THE WORLD

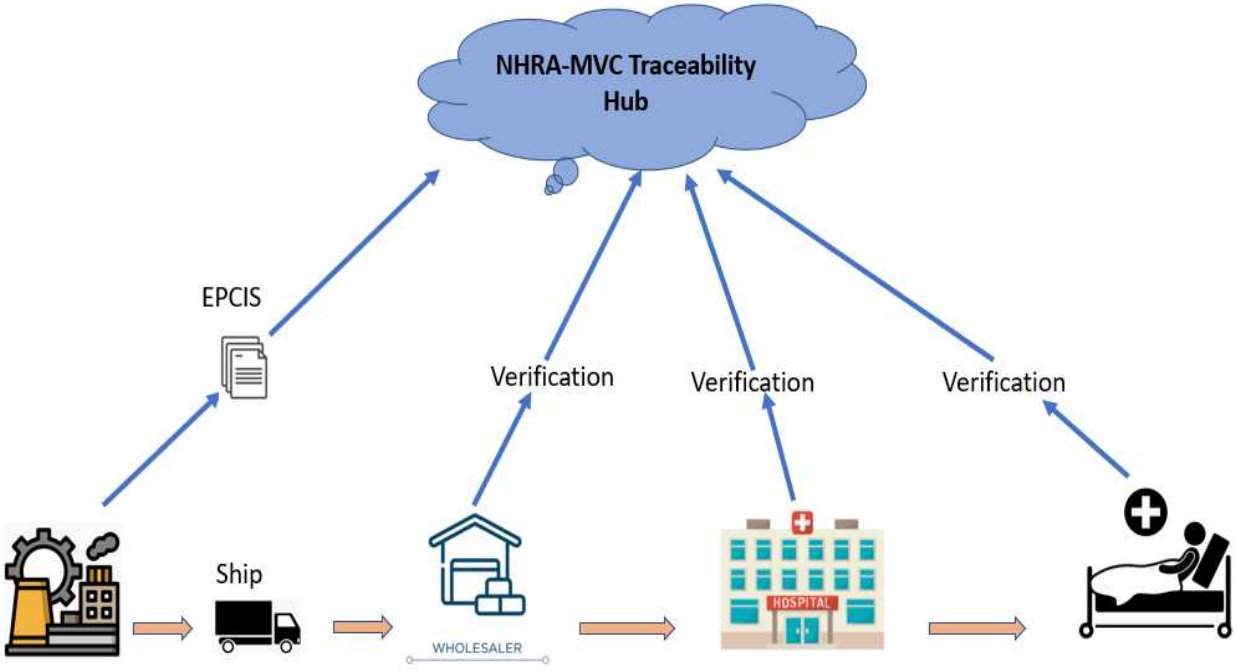
Presently, world-wide regulatory agencies are adopting serialization compliance and implementing track and trace system for medicine traceability. Subsequently, International Council of Harmonization (ICH) which was founded in 1990, promoting public health awareness through implementation of guidelines. The World Health Organization has launched Global Monitoring and Surveillance System (GSMS) to report and track counterfeit medicine in 2013 [14]. Implementing serialization traceability process in the supply chain is not the new concept. Turkey has implemented Pharmaceutical Track and Trace System (PTTS) successfully back in 2013. As per regulation, each product unit must be encoded with unique 2D Data matrix code [15]. Some countries such as China, South Korea have serialization traceability regulation in place. In China, all pharmaceutical drugs will have unique number which will be allocated to manufacturer by regulatory authority [16]. The Saudi Food and Drug Administration (SFDA) mandated any prescribed medicine manufactured or exported in Saudi Arabia must have unique identifier in each prescribed serialization packets as per GS1 standard [17]. Subsequently, The National Health Regulatory Authority in Bahrain, also mandated that individual pharmaceutical drug package must bear following information.

- • GS1 Global Trade Item Number (GTIN) (14-digit fixed length with application Identifier 10)
- • Expiration Date in YYMMDD format with application identifier 17
- • Serial Number up to 20 characters length with application identifier 21
- • Batch or Lot Number with application identifier 10

GTIN, Unique Serial Number, Batch and Lot Expiry. It also must record every activity of drug.

including commission, aggregation and ship events for complete traceability.
All product which is imported to or manufactured in Bahrain, must upload unique serial number into NHRA-MVC Traceability Hub. All stake holders including wholesaler, distributor, dispenser, pharmacy and hospital must verify unique identifier of product during dispense to consumer [18].

FIGURE 1. BAHRAIN TRACEABILITY HUB



• ISSUE IN PHARMACEUTICAL DRUG SERIALIZATION

Pharmaceutical serialization is very stringent and controlled regulatory process for mitigating the risk of counterfeit product. China and Turkey have already initiated serialization process back in 2013 whereas developed countries like United States and Europe implemented serialization process in 2018 and 2019 respectively. Ultimately serialization process mandated to print unique product identifier with 2D Barcode on individually product. Printing 2D barcode with unique identifier on product packaging provides easy function to any stake holders in supply chain to verify the authentication of product. Now days, many manufacturers are facing difficulties for implementing serialization regulation as they are heavily dependent on their legacy system. Further data migration from legacy system to traceability system is another complicated task. Some manufacturer reported to invest approximately 50 million on creating the capabilities of serialization compliance [19].

Another biggest challenge for implementing pharmaceutical serialization is manufacturer or the supply chain stake holders needs to generate, capture and share serialized event data with customers and regulatory bodies. Ultimately data must be share in secure and stringent network. Any compromise with data leak in network further leads an opportunity to criminals and counterfeiters [20].

Implementing serialization regulatory compliance is costly process as it needs investment in many areas including packaging equipment's, packaging software, printer, RF scanner, additional manpower. In developing countries, many pharmaceutical manufacturing companies does have budget to adopt serialization compliance due to low profit, competition, unskilled manpower and inadequate infrastructure. Furthermore, manufacturer also needs acquire additional packaging space for installing specialized packaging equipment's, label grading system and palletization system [21].

• TECHNICAL ADVANCEMENT IN PHARMACEUTICAL SERIALIZATION

Under the serialization regulation, only prescribed medicines are in the scope of serialization compliance. Many instances, it has been noticed that serialization laws are non-impactful without stringent law and regulations. It gives an opportunity to criminal and counterfeiters to supply illicit product in the supply chain. Digital drug traceability plays a crucial role to mitigate the risk of counterfeit drug by verifying the drugs authenticity. Pharmaceutical supply chain stake holders can adopt a secure and reliable blockchain technology to counter the fake drugs supply in legal market [22].

• FUTURE OF PHARMACEUTICAL SERIALIZATION

The Pharmaceutical serialization is complex regulatory process as it needs to ensure the drug security and traceability in the supply chain [23]. In this regulation, wholesaler, distributors and dispenser need to unit level aggregated data electronically in interoperable manner [24].
The DSCSA currently assessing the benefit of Block-chain technology in drug supply chain to secure medicine security and traceability. In this pilot project, DSCSA expected to authorize pharmaceutical industry to provide authentic information directly to their patient in real time basis. The patients can use web and mobile based application to scan barcode from drug packaging and validate the information's. This process will allow patient to have real time drug information and validate the products authenticity. Further it will ensure product information transparency, security and safety in supply chain [25]. Furthermore, this technological advancement will also allow all stakeholders in supply chain partners to collect useful traceability data for stringent solution building for serialized data exchange electronically in interoperable manner [26].

- **Conclusion:**

The Healthcare industry is very critical for human life. It provides life-saving care and treatment to patients by providing secure and authentic drugs. Finally, it is goal for healthcare industry and professional to ensure every patient is getting right treatment. The drug invention life cycle till final approval from regulatory authority goes through many stages including clinical trials, investigational reports, marketing strategies, defining GMP processes and creating standard operating procedures [27] The pharmaceutical drug serialization ensures every patient are getting authentic and secure drugs. There have been significant improvements in drug authenticity since serialization regulatory compliance has been implemented in US, Europe and other part of world. The number of adverse events has been reduced drastically. Unfortunately, the pharmaceutical drug serialization is complex and expensive process. It creates significant challenges for small drug manufacturers as they might have insufficient budgets to implement new compliance. There are many other factors which create difficulties for pharmaceutical industries to implement regulation such as under developed infrastructure, insecure technology, geopolitics, corruptions, lack of political willingness, social and economic imbalance in society [28]. In recent years, most of government and regulatory authority became vigilant for counterfeit and illegal drugs. They are taking many steps and implementing stringent laws against counterfeiting. The drug serialization process with block-chain based traceable technology will create almost impossible for criminals and counterfeiter to supply illegal drug in supply chain [29].

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