ISSN: 2577-2996

PROGRESS IN MEDICAL SCIENCES, 2024
VOL 8, NO. 5, PAGE 1 – 5
DOI: doi.org/10.47363/PMS/2024(8)E117

REVIEW ARTICLE

Open Access

Serialization And Aggregation Solution Overview to Combat Counterfeit Drugs in The Pharmaceutical Industry

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ABSTRACT

Counterfeit medications can be a real threat to patient safety. It is estimated the counterfeit drugs have increased year over year to provide approximately $200 billion in revenue annually to illegal operators and have caused approximately 1,000,000 deaths each year. In one incident, international authorities seized 25,000,000 counterfeit medicines in just one week. Almost every pharmaceutical manufacturer and its associated supply chain partners have been affected by counterfeited and diverted medicines. In response to these global incidents, the government agencies have implemented serialization and track and trace requirements to protect patients.

Anti-counterfeiting and diversion events impact the physical end-to-end pharmaceutical supply chain from the packaging site to the final patient. Pharmaceutical, parenteral and biologic products subject to external venerability throughout their transportation between packaging, distribution or customer sites. To combat counterfeiting and diversion, countries and their government agencies are adopting complex track and trace serialization models to protect patients.

ARTICLE HISTORY

Received September 02 2024
Accepted September 09,2024
Published September16, 2024

KEYWORDS

Serialization, Aggregation, Track-and-trace, Compliance, Counterfeit Medication

Introduction

Counterfeit drugs pose a significant threat to global public health and reduce the public confidence in the robustness of the pharmaceutical supply chain. The World Health Organization (WHO) estimates that one in ten medical products in low- and middle-income countries is substandard or falsified, leading to ineffective treatments, and thousands of preventable deaths each year [1]. To counter this growing threat, regulatory agencies worldwide have implemented stringent measures to ensure the integrity of pharmaceutical supply chains. Prime amongst these measures are the introduction of technology enabled serialization and aggregation solutions in the pharmaceutical supply chain, which have become mandatory in many regions, including the United States, Europe, and parts of Asia. Serialization involves assigning a unique identifier, typically a barcode or a QR code, to each product unit, allowing for individual tracking through the supply chain. Aggregation extends this concept by linking individual units to their packaging hierarchies, such as cartons, cases, and pallets, providing a complete and verifiable chain of custody to all stakeholders in the supply chain. The implementation of serialization and aggregation offers significant benefits, including improved traceability, enhanced recall efficiency, and greater protection against counterfeiting. However, pharmaceutical companies face substantial investments in technology, changes in packaging processes, and the need for extensive data management and integration with existing systems. Despite these challenges, the long-term benefits, such as increased patient safety, regulatory compliance, and reduced risk of counterfeit drugs entering the supply chain, make serialization and aggregation essential components of the modern pharmaceutical supply chain processes.

This research article aims to provide a comprehensive overview of serialization and aggregation solutions, exploring the challenges and benefits associated with their implementation.

Human Harm

Over the years, there have been several events where counterfeit medication has caused significant harm to human health, posing a serious global public health threat. Incorrect ingredients, improper dosages or unregulated/dangerous components has led to severe health consequences, and even death. One of most tragic occurrences took place in 2019 in Cameroon where hundreds of children died due to counterfeit antimalarial drugs. Due to the lack of sufficient dosage of the active pharmaceutical ingredient, the drug was not effective against the disease and increased the mortality rates amongst pediatric malarial patients. Sub-Saharan Africa remains a hotspot for counterfeit anti-malarial drugs, with an estimated 30-60% of all anti-malarial drugs being fake or substandard, significantly impacting malaria control efforts [2].

Another similar high-profile case of inadequate active ingredient was the widespread distribution of counterfeit versions of the antiviral drug Tamiflu through online and unregulated channels during the H1N1 pandemic in 2009 which left many patients

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unprotected against the virus. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that about 92 thousand overdose deaths occurred in 2020 driven by the ongoing opioid crisis that has been exacerbated by counterfeit medications laced with fentanyl, a powerful synthetic opioid [3].

The global nature of the counterfeit drug trade, often facilitated by online sales and weak regulatory enforcement in some countries underscores the need for international cooperation and stronger regulatory frameworks to combat this threat. Pharmaceutical manufacturers and other industry stakeholders are increasingly investing in technology solutions such as serialization and aggregation of pharmaceutical products to disable the entry of counterfeit drug products in the supply chain. Countries around the world and their respective health agencies are taking action to counter the alarming rise in the proliferation of counterfeit medications and medical devices.

After almost a decade of enactment by the US Congress, the Food and Drug Administration flipped the switch on the Title II of the 2013 Drug Quality and Security Act also famously known as the Drug Supply Chain Security Act (DSCSA) to make it an enforced law in November 2023. Through the DSCSA, any finished pharmaceutical products entering the United Sates now have a national, uniform, certified and secure chain of custody by means of standards and processes for end-to-end product tracing, verification and identification from the manufacturer to the customer's prescription.

Basic elements of a pharmaceutical serialization solution

GS1 is a neutral, non-profit global organization dedicated to the design and implementation of global supply chain standards and solutions including the ones employed in the pharmaceutical industry. GS1 standards improve the efficiency and visibility of supply and demand chains globally across an ecosystem of trading partners, industry organizations, governments and technology providers. These standards provide a common language and help to create seamless work processes that allow businesses to identify, capture and share information in a common format across the globe. The GS1 general specification is the core standard document of the GS1 system describing how GS1 barcodes and identification keys should be used.

Here are some of the commonly used serial number terms for product packaging

- The Global Location Number, although not used on product packaging, can be used by companies to identify their locations, giving them complete flexibility to identify any type or level of location required.
- The Global Trade Item Number (GTIN) uniquely identifies the type of product for sale, but not a single instance of that product (e.g. unit of sale). A GTIN is made up of 14 digits
  - o An indicator digit also known as the 'packaging indicator' used to identify various packaging configuration options of the same product. This digit is internally allocated by the manufacturer to each grouping of a trade unit such as 0 for a bottle, 1 for a bundle, 2 for a case etc.
  - o The GS1 authorized company prefix varying from 6 to 9 digits.
  - o For a fee, the NDC Product Code and Package Code can be incorporated into the GTIN. NDC Product Code is part of the National Drug Code (NDC) and identifies the strength, dosage form, and formulation of the drug. NDC Package Code, also a part of the NDC, denotes the package size and types
  - o The check digit is the last digit and used for error detection, and to verify that barcode has been entered accurately. It utilizes a specific mathematical model to compute a single digit based on other digits in the barcode.

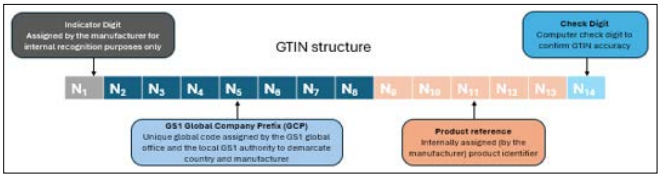

Figure1: GTIN structure

A Serialized GTIN or sGTIN is simply the combination of Global Trade Item Number and a unique serial number (maximum 20 characters). This GS1 supply chain identifier is a context dependent feature of the GTIN that is used to identify individual instances of a GTIN for supply chain purposes on various packaging levels. (example bottle, carton, etc.) and this makes the product truly unique. For example, a GTIN may identify a '90 tablet bottle' of a drug and all the bottles (90 tablet) of the drug will carry the same GTIN. However, each individual bottle will have a unique serial number and, therefore, a unique sGTIN.

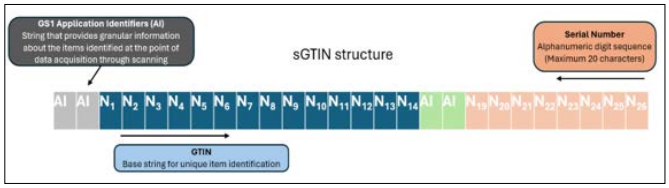

Figure2: sGTIN structure

The serial shipping container code (SSCC), although not used to identify individual units of sale, is the globally unique 18-digit GS1 identification number used to identify individual logistics units at the case picked to order, a mixed case of items picked to order, or a pallet. This SSCC is mandatory on the GS1 Logistic Label and serves as a 'license plate' to facilitate simple tracking of the logistics unit. Suppliers/ shippers are usually responsible for assigning SSCCs to their logistics unit.

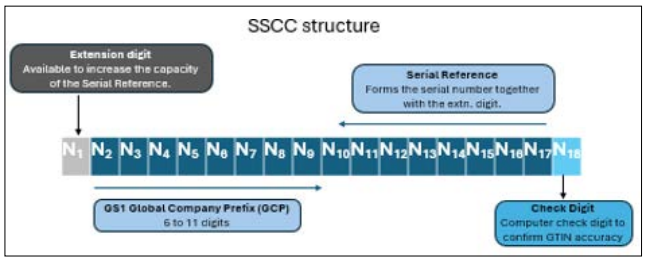

Figure3: SSCC structure

Before discussing the details of the serialization and aggregation solution, we must also look at the various packaging types/steps that a finished product undergoes before being shipped. The following figure captures these packaging steps in order which may be performed internally by a manufacturer or with the help of contract manufacturers and logistics partners in the pharmaceutical supply chain. Serialization can take different

forms and formats depending on the level of product packaging.

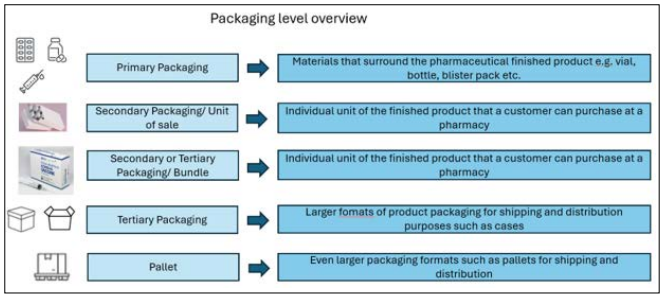

Figure 4: Pharmaceutical packaging levels

The below table provides an overview of various serialization labeling solutions that can be applied to orders received and packaged in different packaging forms/levels.

Labeling applied to different packaging levels

		Homogenous				Heterogenous		
		All packaging contains the same product. sGTIN labeling may be applied for all packaging levels except Pallet.				Due to various reasons, warehouse may restructure packaging to contain multiple types of products. Only SSCC labeling may be used.		
Packaging Type	Secondary	Bundle	Full Case	Partial Case	Pallet	Case	Pallet	Partial Case
Label Type	sGTIN	sGTIN	sGTIN	SSCC	SSCC	SSCC	SSCC	SSCC
Description	Single saleable unit of product in secondary packaging	Multiple units of the same product	Multiple units or bundles of the same product	Incomplete case with multiple units or bundles of the same product	Multiple cases all packed with the same product	A packed case with multiple product types	A pallet loaded with multiple cases with an overall heterogenous composition	A case with multiple product types and partially packed with more space available

Figure 5: Mapping of pharmaceutical packaging levels and serialization labeling solutions

Each level in the serialization process ensures that pharmaceutical products can be tracked, traced, and authenticated as they move through the global supply chain. The following figure captures the serialization system levels that may exist in an organization.

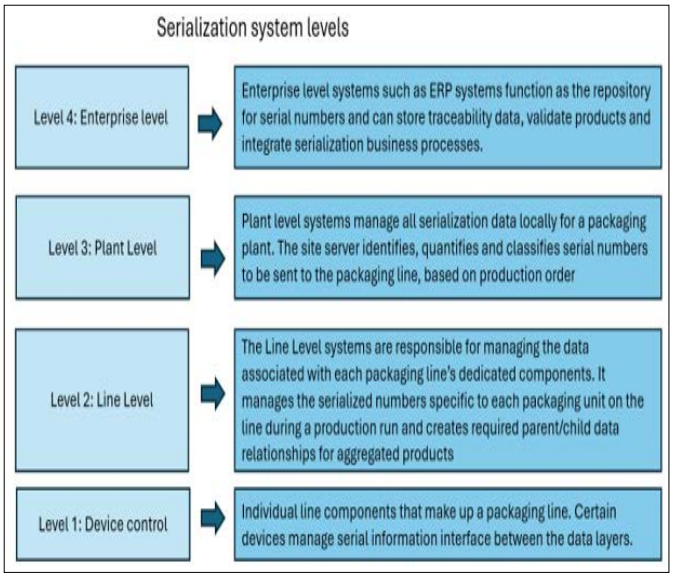

Figure 6: System levels in a serialization solution

Serialization is applied initially at the unit of sale level with a unique number to each product, that can be used to track it from the packaging site throughout the supply chain as products enter the packaging line.

Each organization employs an enterprise level system that generates a pool of potential serial numbers, either internal or external, that can be applied and is sent to the site level and subsequently the packaging line level system. Through the packaging process, each product will be assigned a unique serial number included in a 2D data matrix, also known as a barcode serialization. Labeling can also be extended to bundle, case and power packaging labels. As products progress through packaging, serialization is followed by aggregation, where the serial numbers of individual units are linked to their parent packaging (e.g., cartons, cases, pallets), creating a parent-child relationship. This aggregation allows the product to maintain its hierarchy, providing compliance with track and trace regulations and enabling electronic visibility across the supply chain, even when products are transferred to third-party vendors or distributed to trading partners.

After required product validation procedures are completed, the serial number data is reported back to the Enterprise Serial Number Repository to activate the serial number status in the system. Moving forward, the physical products sanity and serialization status must align with the data stored across serialization systems at all points during the product life cycle and supply chain and the most prevalent track and trace model. When orders for products are received from customers, distribution specialists will prepare the outbound orders by breaking down the pallets to fulfill the order quantity. Order profiles may be homogeneous or heterogeneous. Aggregation allows warehouse team to capture which serial number ships to customers during the order fulfillment process by scanning the serialized barcode at the highest available packaging level required to fulfill the quantity. When shipping a product to a trading partner, the associated product serial numbers may need to be sent to the trading partner's database based on regulatory requirements. Certain markets may also require the serial numbers to be reported to the Regulatory agency database. At the trading partner facility, the aggregation hierarchy is maintained and may be further broken down as they fulfill orders for their customers. As the trading partnerships product and downstream customers, they may need to report the associated serial numbers to the customer's database and or to the regulatory agencies database. As hospitals and pharmacies dispense products to the patient, some regulations require the authenticity of the product to be confirmed before dispensing or dosing application. In these instances, the product is scanned, and the regulatory agencies database is checked to provide a positive verification prior to dispensing or dosing of the product to the patient. The complexity of serialization and aggregation from the product coming off the packaging right to being dispensed to the patient requires close attention to the physical and electronic world. This complexity is expected to increase with upcoming and emerging regulations, with aggregation becoming a requirement for approximately 90% of pharmaceutical products by 2024.

forms and formats depending on the level of product packaging.

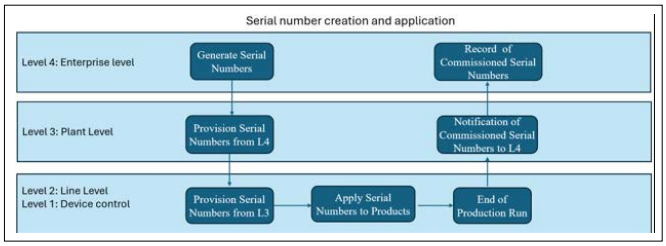

Figure 7: Serial number creation and application

Implementation challenges

Manufacturers and other stakeholders face heavy penalties for non-compliance with regulations in the DSCSA. Failure to comply to DSCSA is a 'prohibited act' as stated in DSCSA section 206 and selling non serialization prescription drug product is classified as misbranding [4]. Simply stated, a company and the concerned persons selling non-serialized prescription drug product face criminal justice along with heavy fines, license suspensions and even imprisonment as is evident by the cases filed by the FDA Office of Criminal Investigation.

The stakes are high, and pharmaceutical manufacturers, and other supply chain stakeholders have faced a lot of hurdles over the last few years as they look to become compliant and follow the associated deadlines. Although the regulations define the serialization solution, requirements, and processes, they don't necessarily provide guidance on how to implement this solution. Lack of standardized data formats to capturing aggregated track and trace information for easy sharing across the partner ecosystem in the global supply chain also hampered the progress of any organization looking to implement serialization solutions. Serialization also adds to the complexity of existing production and warehouse management processes. Extra layers and volume of serialization data must be incorporated into various master data objects, interfaces with boundary systems, and supply chain reports. The serialization solution and associated data must flow seamlessly between enterprise resource planning (ERP), manufacturing execution systems (MES), track and trace systems, and warehouse management and associated shipping systems. Designing, validating and implementing a solution to this level of granularity and integration can be quite challenging and resource intensive for any organization. Coordination with multiple internal manufacturing or warehousing facilities, contract manufacturers, logistics partners and customers necessitate meticulous project planning and execution. The sheer magnitude of solution implementation for firms with extensive portfolios, and intricate supply chains can cause multiple delays along the journey to full compliance. Since the initial 2013 enactment of DSCSA by the US Congress, organizations also had the challenge to track these regulations along with their dynamic requirements and build necessary internal teams across departments–regulatory and compliance affairs, legal, IT, manufacturing, logistics. This complexity, combined with Covid related disruptions, and a lengthy FDA process had instilled a 'wait and watch' attitude amongst organizations in the prior years with inhibitions to upfront commitment to investment. However, the end of FDA's 'stabilization period' in November 2024 has organizations scrambling to complete process and technology implementation.

The serialization solutions put in place by manufacturers have impacts on downstream partners as well. Logistics partners (3PLs or 4PLs) now need to stand up to the operational challenge of verifying the authenticity of received serialized product, including checking the UPI and transaction history of every serialized lot. All the internal processes of pick, pack, storage, transportation must now be aligned to ensure the integrity of the UPI [5]. Market leading logistics services providers now provide serialization and aggregation compliance support as a service to their manufacturing partners which include the ability to request/receive/ generate serial numbers, EDI integration, and data repository support. Similarly, other stakeholders such as wholesalers or dispensers also require becoming DSCSA compliant and undertake infrastructural and personnel upgrades to maintain UPI integrity.

Benefits Beyond Compliance

In addition to regulatory compliance and reduction in counterfeit medications, pharmaceutical supply chain players stand to benefit from product serialization and aggregation in other aspects of business as well. The same technology and process investments for compliance with serialization can also enable enhanced supply chain visibility traversing the internal supply chain of an organization. Products can now be traced all the way through logistics and distribution to the end customer thus providing the ability to derive metrics on product movement, order fulfillment, delivery times, failure rates etc. Organizations can also leverage open standards such as Electronic Product Code Information Services (EPCIS) which allows for capture of product movement and status data both internally and externally, and ultimately share this data with EPCIS global network participants to gain a shared view within a business context [6]. Since the individual units can be easily tracked and identified, recall management processes also gain efficiency. Improvements in supply chain data volume and accuracy, and downstream reporting with minimal human intervention also enable organizations to leverage advanced analytics to understand logistical/ consumption patterns and make long term, strategic decisions. For an organization that is serialization capable and compliant in multiple markets, it may be easier to launch new products in a shorter time and prevent any potential revenue losses. Prevention of entry of counterfeit medication in the supply chain also has significant cost containment effects since the organization no longer has to deal with expensive recalls, legal issues, or brand damage.

Conclusion

Almost every pharmaceutical organization has had historical cases of high value medication being diverted to the streets or for personal use by means of theft, hijacking, improper storage or product alteration to add volume and profits. Serialization and aggregation have emerged as critical solutions in the face of the increasing global threat of counterfeit medications offering a powerful means of tracking and verifying pharmaceutical products throughout the supply chain. Despite the clear benefits, pharmaceutical manufacturers must assess the costs, and the implementation challenges associated with investing in new technologies, adapting packaging equipment and processes, and developing appropriate data management systems. However, all the associated costs and complexities of serialization and

aggregation solution implementation are arguably beneficial in the long term for pharmaceutical supply chain stakeholders with improved patient safety, regulatory compliance and increase robustness of the supply chain. The global pharmaceutical supply chain is hard at work implementing these solutions to ensure that patients receive legitimate pharmaceutical products while maintaining trust with healthcare providers [7].

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