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## Implementation Challenges of Global End-To-End Traceability System for Pharmaceuticals in Low and Middle Income Countries: Literature Review

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### Abstract

#### Background

Aligning around a single set of global standards can support processes and capabilities that create value for all participants in a supply chain, from business partners down to the patients. Serialization being a new concept very little is known about its impact on domestic producers in developing countries.

**Objective**

To identify the bottom line impact of applying global serialization standard on young domestic pharmaceutical production companies in developing countries.

**Method**

We have reviewed available literatures, directives, guidelines and manuals of different countries, conference proceedings and reports available online.

**Finding Description**

Being a new technology we couldn't find enough evidence to show the clear impact of global GS1 serialization in domestic producers of developing countries. Based on our review domestic producers in low and middle income countries should evaluate their capacity before implementing the global standards in their immature industries. Therefore, it is worth to improve the countries border control, transparency of supply chain and national drug quality control laboratory capacity for their domestic production and designing their own supply chain visibility system to address the imported products based on their own capacity than struggling with global serialization system is imperative. GS1 serialization should be considered in strategic plans of all pharmaceutical supply systems in these countries. This is because the future distribution will be based on the Global standards as diffusion in technology and human capacity development in the area improves.

**Introduction****Background Definitions**

Maintaining the supply chain integrity of pharmaceuticals is vital for ensuring quality of healthcare delivery. Drugs are indispensable components of healthcare delivery. Substandard and counterfeit medicines are challenges of 21<sup>st</sup> healthcare system with estimated prevalence of 20-40% in developing countries and about 1% in developed countries. This is because development and transportation of drugs is complex and involving multinational companies and borders of different countries. A single pill might pass through a dozen countries during its manufacturing process, which offers many opportunities for criminals to put fake drugs into the supply chain. For example, chemicals synthesized in China can be combined with fillers in India and then packaged in Mexico before arriving at a pharmacy in Canada and may be used by Ethiopian who has requested his friend in Canada to buy the drug for his illness due absence of the drug in Ethiopia [1].

In addition to this complex nature, drug trafficking is highly lucrative business and smugglers are financially and technically well equipped to extent that there is no system to break their extensive international networks. Weakness of the pharmaceutical regulatory system in developing countries, shortage of essential drugs, unaffordability, leaky supply chain systems and community awareness are fuels for increased counterfeiting and smuggling in Developing countries. While in developed countries, e-commerce and long handed

smugglers network are contributing to the problem. Therefore, it is important to secure and protect these more complex and interconnected global pharmaceutical distribution networks [2].

Tracking and tracing of products in supply chain is designed to prevent the manufacture and sale of the counterfeit medicines, implement a system to detect any such product that is the supply chain already and respond quickly to any incidents to make sure the patients are safe and the supply chain is clean [1,2].

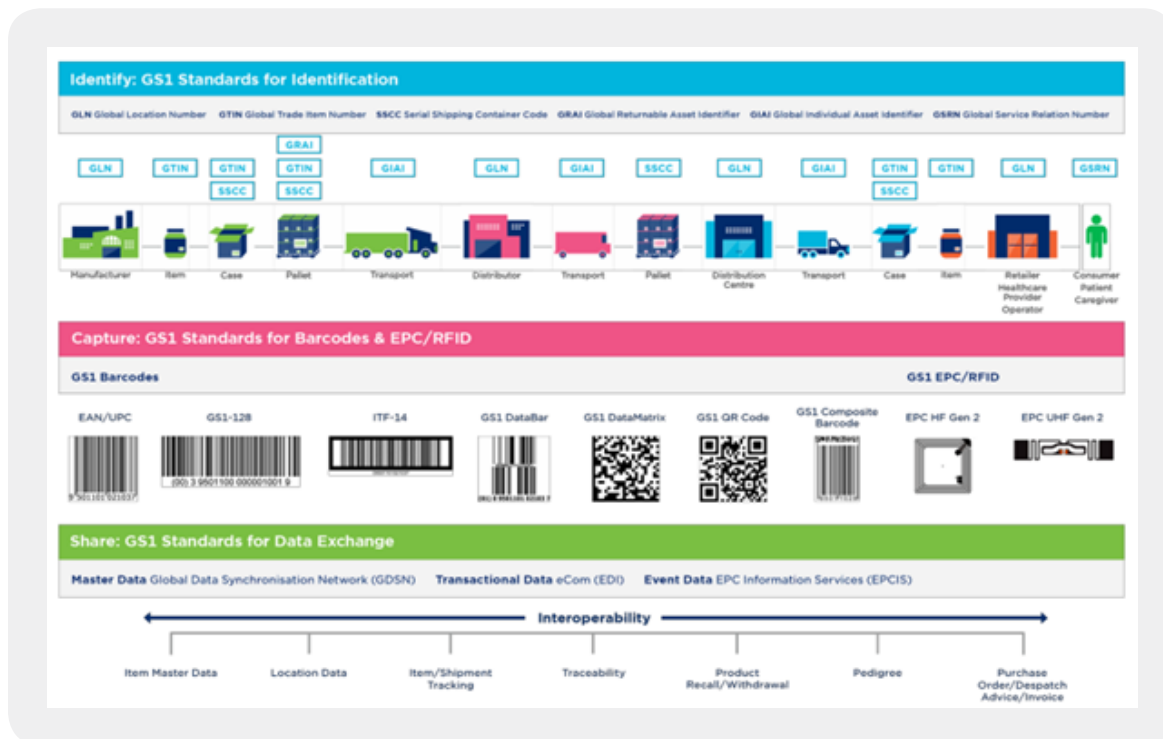
Serialization is the process by which products are marked with a unique identifier typically a unique number or alphanumeric code and is beginning to be leveraged to enhance supply chain security. The unique serial number, along with other related information, is typically encoded in a barcode that can be read electronically. Serialization itself provides virtually no benefit to the supply chain; rather it is the use of that serialized data in a traceability system that enhances supply chain security. The infrastructure and processes that leverage serialized data in some manner to improve supply chain security are collectively referred to as a “traceability” or “track and trace” system [3].

Aggregation is tracking of parent/child relationships from unit level to case, and case to pallet. It is important because wholesalers and third-party logistics providers (3PL) need the capability to infer contents of pallets and cases to conduct their business efficiently, they are requiring serialized product to be aggregated. Without aggregation and inference, wholesalers and 3PLs would need to break down all packaging levels to the smallest saleable unit to determine which unit-level serial numbers are involved in a transaction. Therefore, aggregation is required by many trading partners and is becoming the industry standard [4].

Although serialization requires large investments of time and resources, with the appropriate infrastructure and technology, the data acquired from serialized product can be leveraged to address challenges that countries face, such as counterfeiting and diversion, by increasing visibility and control in the supply chain. Further, knowledge of product location and product owners throughout the supply chain can help identify where an illegitimate product entered the legitimate supply chain or can allow for more precise and rapid recall of pharmaceutical products if necessary [5,6].

### **GS1 is a System of Global Standards for the Health Supply Chain**

GS1 standards enable traceability of items in the supply chain: Low-precision identification; Medium-precision identification; High-precision identification; Item exists in multiple locations at the same time; Item exists in only one location at the same time; Enables inventory control; Enables anti-substandard and falsified (SF) measures and Enables product recall [7]. The GS1 system of standards is such a system, providing a comprehensive platform for companies to identify products and business entities, capture supply chain data, and share data with trading partners. GS1 standards encompass identification standards, data standards, and automatic identification data capture (AIDC) standards such as barcodes. Figure 1 below summarizes some of the GS1 standards that support supply chain management and data visibility [7].



*Figure 1: GS1 standards for identification adopted from Implementation Guidance for Pharmaceutical Traceability Leveraging GS1 Global Standards. February 2019.*

### Traceability and End-to-End Visibility

Both traceability and end-to-end visibility are two faces of one coin in maintaining supply chain security. The main objective of traceability is to track movement of products across the supply chain to improve supply chain efficiency and verify products to remove Substandard and Falsified medicines and improve patient safety Scope While the objective of end-to-end visibility is to Ensure data visibility from planning until delivery of products/commodities to enhance decision making and Monitor execution to guide every task and manage supply chain exceptions (Table 1) [7].

*Table 1: Difference between end-to-end visibility and traceability adapted from reference [7].*

	<b>End-to-End Data Visibility</b>	<b>Traceability</b>
<b>Objective</b>	<ul style="list-style-type: none"> <li>• Ensure data visibility from planning until delivery of products to enhance decision making</li> <li>• Monitor execution to guide every task and manage supply chain exceptions</li> </ul>	<ul style="list-style-type: none"> <li>• Tracking movement of products across the supply chain to improve supply chain efficiency</li> <li>• Tracing where products came from and where they went to facilitate product recalls</li> <li>• Verifying products to remove Substandard medicines</li> </ul>

<b>Scope</b>	<ul style="list-style-type: none"> <li>Strategic, tactical, and operational</li> <li>Processes and data related to supply chain as well as physical product movement</li> </ul>	<ul style="list-style-type: none"> <li>Operational and transactional</li> <li>Processes and data related to physical product movements</li> </ul>
<b>Level of Detail</b>	<ul style="list-style-type: none"> <li>Data aggregated at the product level</li> </ul>	<ul style="list-style-type: none"> <li>Data at GTIN, batch/lot, and serial number levels of granularity</li> </ul>
<b>Benefits</b>	<ul style="list-style-type: none"> <li>Manage supply chain exceptions</li> <li>Facilitate better decision making in planning</li> <li>Provide better coordination across supply chain enabling efficient resource allocation</li> </ul>	<ul style="list-style-type: none"> <li>Ability to locate products accurately through different supply chain stages</li> <li>Improved patient safety</li> <li>Elimination of counterfeit products</li> <li>Ability to recall products effectively</li> </ul>

**Benefits of Serialization**

A serialization investment can deliver numerous benefits for manufacturers. Beyond compliance with the federal government, serialization helps protect consumer safety through proper labeling management of packaging processes hence reduce risk of counterfeiting. This can help protect brand reputation by increasing patient safety. With serialization, manufacturers can capture necessary information while a product moves through the supply chain. This enables them to improve efficiency, control costs, and increase shipping accuracy, ensuring recall integrity. When a company has an understanding of the supply chain process, it can more easily control inventory and drive better understanding of the impact of disruptions. Additionally, serialization helps companies minimize chargebacks associated with packaging errors and claims against pharmaceutical manufacturers (Table 2) [7].

*Table 2: Showing Traceability supports for supply chain objectives*

		Patient Safety	Supply Chain Security	Supply Chain Efficiency	Data Visibility
Address	Substandard or Falsified/SF or stolen products in the supply chain				
	Theft or diversion of products from the legitimate supply chain				
	SF or stolen product that is obtained by the patient/end user				

Improve	Accuracy and efficiency of procurement operations				
	Visibility of product “status” (e.g., expiry, recalls)				
	Efficiency of “reverse” logistics processes				
	Efficiency of inventory management and distribution				
	Efficiency of payment and payment monitoring processes				
	Pharmacovigilance and control of treatment outcomes				
Enable	Visibility into where the product is within the supply chain				
	Visibility to decrease or eliminate reimbursement fraud				
	Harmonized trade clearance procedures for pharmaceutical products				

### Traceability in Healthcare

Aligning around a single set of global standards can support processes and capabilities that create value for all participants in a supply chain, from business partners down to the patient. Advantages of fully functioning end-to-end serialization in healthcare include the following [7-10].

#### 1. Supply Chain Data Visibility

Increasing data visibility can strengthen the supply chain in several ways:

- Improve visibility of product “status” (e.g., expired or about to expire product, recalled product)
- Improve product quality management (e.g., expired and/or recalled products are promptly identified)
- Provide visibility of where the product is within the supply chain
- Reduce data management costs
- Support systems interoperability, allowing access to linked data through identification keys across logistics, clinical services, insurance, and patient applications

#### 2. Increased Patient Safety

Patient safety issues can be addressed through the use of standardized information to:

- Enable medication authentication to remove falsified or stolen product from reaching patients

- Improve recall management effectiveness, reducing the risk of patient harm
- Reduce drug shortages
- Improve pharmacovigilance
- Reduce medication errors, such as inaccurate administration, through bedside scanning

### ***3. Ensured Supply Chain Security and Control***

Global supply chains, including for health commodities, face high security risks due to their complexity and global reach. Reporting movement of products through the supply chain, whether at the batch or unique item level, is important for security management and can allow protection against various threats, including:

- Falsified products
- Theft or diversion of products
- Reimbursement fraud

### ***4. Increased Supply Chain Efficiencies***

The increased data quality from automatic and standardized data capture allows for the following benefits:

- Reduced manual processes in data capture for receiving, inventory management, picking, packing, and dispatching
- Improved ability to capture consumption data, resulting in better informed demand forecasting and inventory planning and reduced inventory management costs
- Improved efficiency and cost of “reverse” logistics processes (e.g., those used for returns, recalls)
- Improved efficiency of payment and payment monitoring processes
- Harmonized trade/customs clearance procedures

### ***5. Improved Trade and Business Across Borders***

Countries' use of their own proprietary identifiers and national/domestic labeling requirements results in higher costs for manufacturers and limits their flexibility to produce larger batch runs to serve orders from multiple markets. Standardized identification and labeling can eliminate this trade barrier by enabling products to be identifiable globally. For domestic manufacturers, use of global standards also increases their ability to compete in other markets.

## **Tracking and Tracing System**

### **Key Stones of Traceability**

There are three underpinnings, which are implemented in various ways, in various forms in the U.S. and in other countries [7,11].

### Serialization

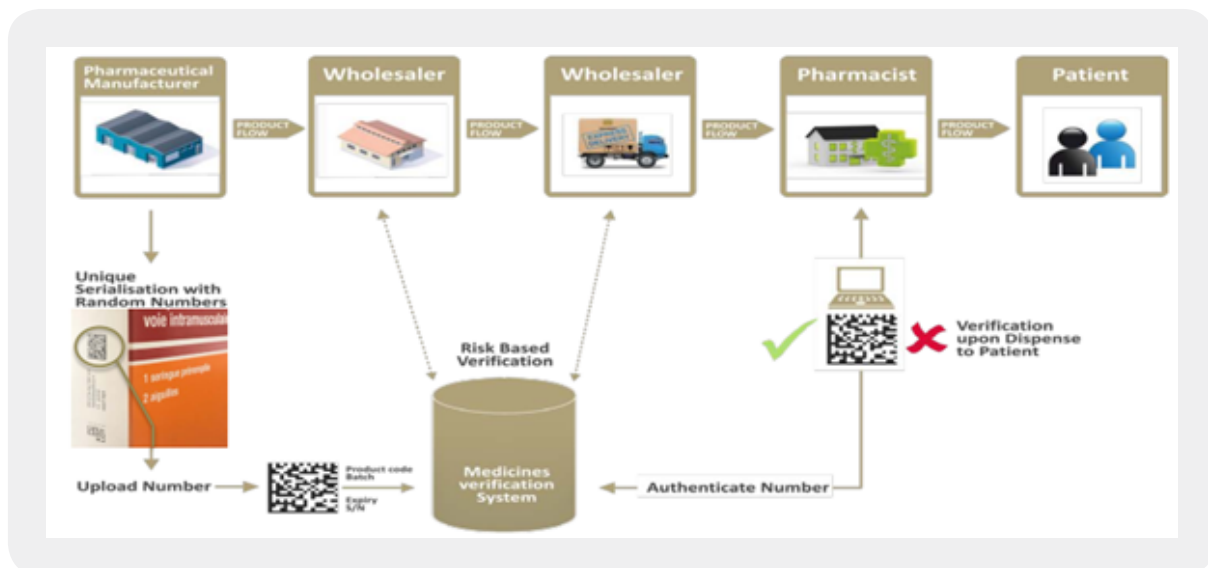
(Unique product via its product identity, Lot number and Expiration date).

### Track and Trace

(tracking a forward view where is a product right now in the supply chain and capturing information about that product as it moves through the supply chain. Tracing is more of a historical view let me see where the product has been or who has owned it).

### Verification

Product verification refers to checking at any single point in the supply chain that the unique identifier printed on the item is assigned by the product manufacturer. Countries can implement verification as part of a traceability mandate or as a point-of-dispense (e.g., check at a service delivery point) and/or point-of-use (e.g., check by the consumer or the patient) model at an end point in the supply chain (Figure 2).



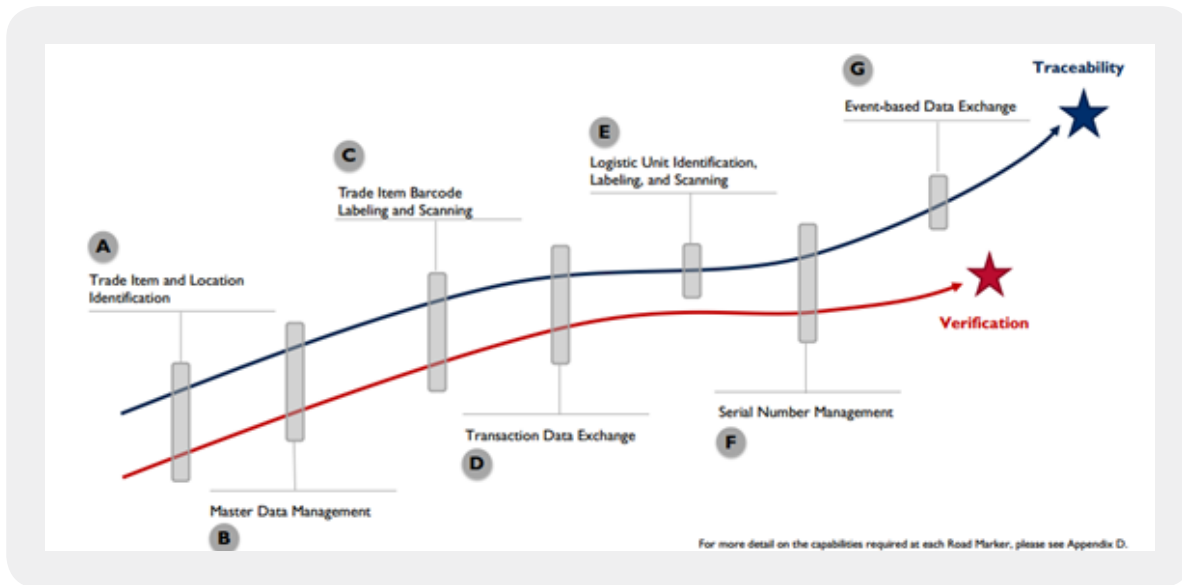
**Figure 2:** Point of dispense Verification European system

Verification requires, at a minimum, that trading partners at the end of the trade item supply chain check the validity of a trade item's unique identifier and update its status (e.g., decommissioned). The common models for verification are defined by the point at which the verification occurs, generally either at the point-of-use (Before use of a product by a patient or consumer, the unique identifier on a product's packaging is validated by comparing it with information provided by the product manufacturer) or at Point of dispense (Before dispense in health centers, pharmacies, or health posts, the unique identifier on a product's packaging is validated by comparing it with information provided by the product manufacturer) [7].



## Roadmap for Tracking and Tracing

Road of tracking and tracing system involves series of components like: Assigning Trade item and location identification, master data management, Trade item barcoding and scanning, Transaction data exchange, Logistic unit identification labeling and scanning, Serial number management and Event-based data exchange (Figure 3) [7,12,13].



**Figure 3:** Road map for tracking and tracing adopted from *Implementation Guidance for Pharmaceutical Traceability Leveraging GS1 Global Standards*. February 2019.

### A. Trade Item and Location Identification

Unique identification of trade items and locations/legal entities is a foundational requirement for verification and traceability as a means to access master, transaction, and event information about items and locations in the supply chain and to share this information with internal and external trading partners. The use of global identification keys like the Global Trade item number/GTIN and Global Location number/GLN by all trading partners facilitates the exchange of information, increasing supply chain data visibility. Helps to ensure that products have a globally unique identification number assigned to them; provide product movement clarity along the entire supply chain and serves as the foundation for procurement accuracy, Good Distribution Practices (GDP), inventory management, verification, and traceability. However, it doesn't meet National coding structures specific countries [7].

### B. Master Data Management

Master data management (MDM) is the process of linking identification data and reference data across multiple systems into a single, consistent point of reference. Master data refers to data that is associated with the product and mostly remains unchanged, e.g. the product description. Global data synchronization

enables healthcare trading partners to share trusted product master data, locally and globally, in an automatic and efficient way. These data are foundational for all items and locations to be used across supply chain business functions, from registration and importation to service delivery. Treating MDM like an information technology project rather than a business strategy that is optimized with appropriate use of enabling technologies is its potential challenge [7,12].

### ***C. Trade Item Barcode Labeling & Scanning***

Barcodes are symbols that can be scanned electronically using laser or camera-based technologies to automatically capture data encoded in the barcode and input it into relevant supply chain information systems, e.g., enterprise resource planning, warehouse management system (WMS), and LMIS. Barcodes play a key role in supply chains, enabling parties like retailers, manufacturers, transport providers, and hospitals to automatically identify and track products as they move through the supply chain. Trade item packages should be labeled with a barcode with a minimal set of key data elements like the GTIN, batch/lot, and expiry date to ensure that these data can be captured and referenced at every point in the supply chain, through to the point of dispense. By scanning the GTIN, the user can also access other item master data stored within a given database. However, developing proprietary barcode labeling is redundant and creates challenges to interoperability and future standards implementation and including more data in the barcode than what is required to enable traceability increases costs for trading partners in applying and using that information [12].

### ***D. Transaction Data Exchange***

Transaction data are any data derived from transactions, such as a requisition order (RO), purchase order (PO), advance ship notice (ASN), stock count, distribution order (DO), or invoice. These are data that is shared between two trading partners in the sale/purchase process (Electronic Data Interchange), e.g. purchase order, delivery note, invoice, payment. Leveraging standards for transaction data exchange is important to enable automation of common business transactions commonly occurring across the supply chain in support of data accuracy and process efficiency. Potential Pitfall this data is scaling too quickly before protocols have been defined and tested with multiple types of trading partners and systems [7,13].

### ***E. Logistic Unit Identification and Barcode Labeling***

A logistic unit is an item of any composition established for transport and/or storage that needs to be managed throughout the supply chain, for example, a case, pallet or parcel. The serial shipping container code (SSCC) is a unique serialized number assigned by and labeled on the package by the creator of the logistic unit. SSCCs are matched with the electronic business messages that refer to them, such as packing slips and advanced ship notices (ASNs), to track them individually to support order and delivery tracking, automated goods receiving, and as a reference number to provide detailed information on the contents of a given unit. The SSCC can be captured when a unit is dispatched, arrives at its destination, and at any other intermediary point during its useful life. The SSCC also serves as a critical identifier for aggregating serial numbers when implementing track and trace. It helps to ensure that every item is uniquely identified on the physical package and in subsequent reference documents. This supports efficiencies in

shipping, receiving, and handling logistic units and their contents. Potential pitfall is Underestimating the role of all logistics providers in being able to generate and manage SSCCs for all logistic units [7].

### ***F. Serial Number Management***

Batch/lot numbers correspond to a certain number of items assigned to a common group of items that were manufactured at the same time. Batch/lot and items have a one-to-many relationship, as many items can have the same batch/lot number. Serial numbers correspond to a unique instance of a given item; the serial number and its item have a one-to-one relationship, allowing an entity to track and trace the item from manufacture to dispense. However, Serialization of items is a significant investment of manufacturers and does not provide a benefit to the supply chain unless the serial number data are used for track and trace or verification. Ensuring stakeholders understand the complexity of the solution proposed and resources required availing adequate infrastructures is important [7,13].

### ***G. Event Data Exchange***

Track and trace requires that different trading partners share information about the physical movement and status of products as they move through the supply chain from partner to partner, and ultimately to the end user. Event data answer the questions “what, where, when, and why?” to meet reporting demands from a range of public health stakeholders, from regulatory authorities to consumers. The GS1 Electronic Product Code Information Services (EPCIS) standard, in conjunction with the GS1 Core Business Vocabulary (CBV), is the global standard for event data exchange to enable disparate applications to create and share visibility event data, within and across enterprises, according to common definitions of data values. Event data exchange enables a complete ledger of item status, custody/ownership, and location over the lifecycle of the item, from manufacturer to dispense. However, it overestimates the capabilities of trading partners to scan and report for all events in scope [7].

### **Take Steps to Stay in the Serialization Race**

There are a number of factors to consider when introducing serialization processes. This include the following: (i) Consider legislative complexities; (ii) Map out your requirements; (iii) Pay attention to timeframes; (iv) Limit your investment; (v) Consider the full drug lifecycle and (vi) Look to the future. It is important not to forget how serialization may impact your productivity going forward. Evidence from early adopters of serialization processes suggests that productivity, also known as overall equipment effectiveness (OEE), can go down by as much as 10% [14]. It is extremely important to map out your internal business process from purchase of material through to the delivery of finished goods to find out where and how serialization will affect your operations. Patient expectation safe and high-quality drugs and manufacturers expectation to ship their products in a secure supply chain that guarantees the custody of these medicines places greater responsibility on distributors, re-packagers and other intermediaries in the supply chain. Creating a tighter and closed system is required to prevent the introduction of illegitimate products, better detect the introduction of illegitimate products, and enable stakeholders and the regulatory organizations to respond rapidly when such products are found [14,15].

shipping, receiving, and handling logistic units and their contents. Potential pitfall is Underestimating the role of all logistics providers in being able to generate and manage SSCCs for all logistic units [7].

## Traceability Models

Several models for traceability in the pharmaceutical industry are currently implemented. Depending on the specific challenges in their pharmaceutical supply chains the scope or phases of implementations worldwide could differ. The models could be a 'centralized, or a 'semi-centralized' traceability system (Table 3) [7].

### Centralized Model (National)

Contain one centralized data repository (hub) at the country level managed by a ministry, regulatory authority, or logistics management unit. Trading partners have to share event data with the central hub and requires data integration with trading partners for data exchange.

### Semi-Centralized Model (National)

Semi-centralized model contains national and sub-national hubs. The National data hub is managed by ministry, regulatory authority, or logistics management unit. External trading partners have to share event data with the central hub and it requires data integration with trading partners for data exchange. While Regional-, zonal- or district level hub manage subnational event data reporting and requires data integration with internal trading partners for data exchange.

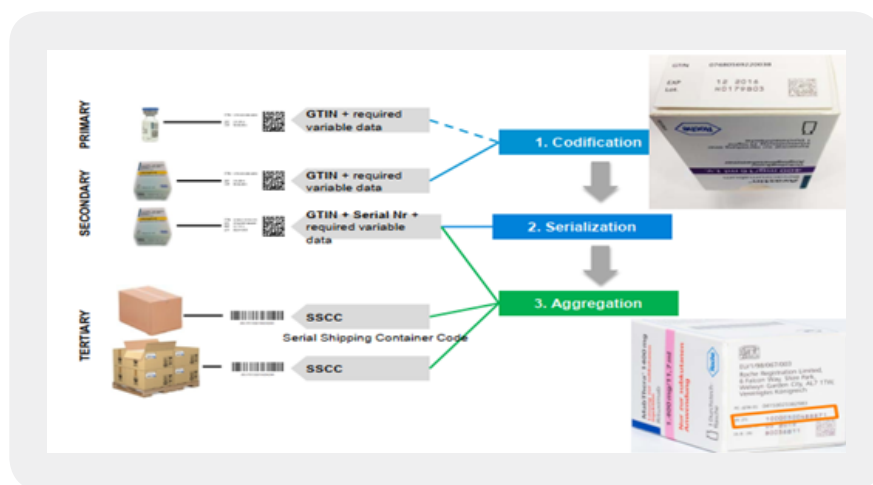
**Table 3:** The difference between Centralized and Semi-Centralized models

	Centralized	Semi-Centralized
Architecture	<ul style="list-style-type: none"> <li>One repository for a country or region</li> <li>All event data are reported into one repository</li> </ul>	<ul style="list-style-type: none"> <li>More than one repository by country, region, etc.</li> <li>Event data are reported into multiple repositories</li> </ul>
Data Security	<ul style="list-style-type: none"> <li>More centralized the data, the greater the security risk</li> <li>Security will be managed by a central authority</li> </ul>	<ul style="list-style-type: none"> <li>Security risk is distributed, but secure solutions need to be managed at multiple points in the supply chain</li> </ul>
Data Sharing and Access	<ul style="list-style-type: none"> <li>Centralized management of data, access &amp; use</li> <li>Data accessed from one central repository by all users</li> </ul>	<ul style="list-style-type: none"> <li>Data reported to and accessed from multiple repositories</li> <li>Need to clearly defined data ownership and exchange protocols</li> </ul>
Governance	<ul style="list-style-type: none"> <li>Less complex with a single repository that can be managed by a central authority</li> </ul>	<ul style="list-style-type: none"> <li>More complex with multiple repositories governed by different entities within a country or across countries</li> </ul>

Ease of Implementation	<ul style="list-style-type: none"> <li>Responsibility for implementation and enforcement resides with a single entity</li> <li>Can take a phased approach with incrementally more reporting incorporated over time</li> </ul>	<ul style="list-style-type: none"> <li>Responsibility of implementation and enforcement resides with multiple entities within or across countries</li> <li>Can take a phased approach with additional hubs onboarding over time</li> </ul>
Interoperability	<ul style="list-style-type: none"> <li>Integrating master, transaction &amp; event data from different partners require use of data standards to support a high level of interoperability</li> </ul>	<ul style="list-style-type: none"> <li>Enabling traceability across multiple repositories requires use of data standards for master, transaction, and event data to support a high level of interoperability</li> </ul>
Benefits	<ul style="list-style-type: none"> <li>Strong centralized coordination and control</li> <li>High levels of visibility across the entire supply chain</li> </ul>	<ul style="list-style-type: none"> <li>Can expand scope of traceability across regions</li> <li>Address challenges related to regional trade and open borders</li> </ul>
Limitations	<ul style="list-style-type: none"> <li>Data visibility will be restricted to items legally imported into the country</li> </ul>	<ul style="list-style-type: none"> <li>Visibility limited to subnational or sub-regional repositories</li> <li>Need to manage risk of items being reported across multiple repositories through the distribution lifecycle</li> </ul>

**Different Measures for Different Purposes**

Different approaches can be used to address regulatory needs of countries. Commonly used include; codification (product identification by the product: GTIN + lot no.+ Expiry date); Aggregation and serialization (Figure 4).



*Figure 4: Different measures for different purposes*

## Steps of Serialization Implementation

Tracking and tracing system success depends on setting right strategies and implementation plans. The country tracking and tracing company/office should have clear goals and strategies to achieve these goals designed by involving all stakeholders having direct or indirect effect on product movement along supply chain. The following are examples of activities that can be done before, during and after implementing the track and tracing system in national pharmaceutical supply chain. [1] Before implementing track and trace program: Communicate Proactively with customers, select right team to lead the program and identify benchmarks. [2] During implementing track and trace program: Develop Strategic plan, Select Vendors and standardize the process by using pilot program at country level [16,17].

Implementing serialization requires self-evaluation of capacity to adopt technologies and available opportunities for running the system. Here are some of steps required to implement serialization in a given country [16-19].

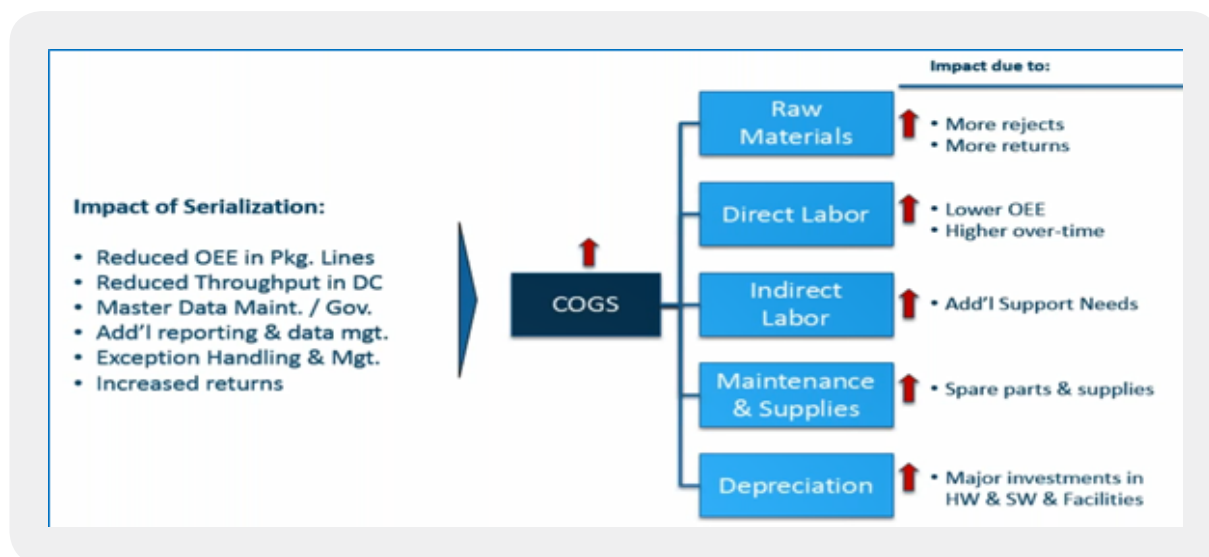
1. Involve all relevant stakeholders
2. Select priority areas (drugs with high risk for counterfeiting, controlled drugs etc.)
3. Conduct pilots before scaling up traceability implementation
4. What to serialize at port of entry (Bulk package, Secondary Package, Primary Package (sellable unit packaging) or individual product)
  - a. Bulk package/Cartoon or pallet serialization
  - b. Secondary package/Box serialization
  - c. Primary Package/Sellable unit serialization
  - d. Individual product/Vial, capsule, tablet Serialization
5. Serialization and traceability of unique items; Implementation of this phase will benefit the pharmaceutical supply chain because:
6. Planning data traceability/visibility goal (regulatory, National warehouse, or dispensing unit or individual patient level)
7. Regulatory requirement: some countries may require changes in existing pharmaceutical laws
8. Quality control of traceability system (Barcode, serial number quality etc.)
9. Monitoring the system performance and scale-up for next priority products

## Global Standards in Low and Middle Income Settings

In recent years, drug regulatory authorities and the health care industry have been aligning on adoption of global standards for identification, including serialization; product labeling; and data exchange to enable pharmaceutical traceability. However, of implementing this global standard in domestic production of low and middle income countries which are struggling with immature domestic production and lack of access to essential medicines will have negative impact on the industry as well as on the healthcare service delivery. This is domestic manufacturers in LLMICs often operate in capital-constrained environments and may have a limited ability to invest in technological infrastructure to support increasing innovation. These constraints may result in additional challenges in meeting the increasing number and stringency of regulatory requirements, including stricter quality standards and quality control measures and, moving forward, implementation of global standards for identification, labeling, and data exchange [20,21].

### Serialization Bottom-Line Impact

Serialization or implementing track and trace system increases the cost of final goods sold, decrease efficiency packaging lines. This is because it increases rejection from raw material sides, reduces overall equipment effectiveness, requires additional human resources and machines and increases depreciation (Figure 5) [6].



*Figure 5: Bottom line impact of serialization*

### Challenges of Serialization Global Standards in LMICs

Track and trace is an area where skilled people are still relatively rare, and where pharmaceuticals companies especially smaller ones are still experiencing difficulties evolving their operating models to comprise more effective exchanges across their organization and with the partners. The following are some of major challenges for implementation of serialization: (i) Financial, (ii) Complexity of structure; (iii) Technology and infrastructure related; (iv) Legislative requirement related; (v) Establishing long-term relationships with

vendors; (vi) Complexity of the pharmaceutical supply chain; (vii) Concern of product safety and quality; (viii) Productivity and Cost Issues and (ix) Data Management Challenges [22].

**Financial: One-Time Investment, Unit-Cost**

Serialization affects every aspect of the pharmaceutical business: proper implementation uses up resources and the impact on an organization should be fully assessed. Not only regulatory offices, supply chain management, engineering and IT systems, but also project management, operations, quality, internal training, packaging and artwork/marketing departments are involved in the process. The creation of a dedicated working group with representatives from all these different areas has proven successful in the deployment phase. Capital investments include the costs associated with acquiring the equipment and technologies for implementation. These represent a one-time investment that can be amortized over time, with expectation of recovery through earnings and costs savings over several years. These costs vary depending on the desired capabilities (more complex requirements often require more sophisticated technologies) and the scale of the solution (e.g., manufacturers with more production lines will require more scanners than those with fewer production lines) [23].

A rough estimate of overall, the European Generics Association (EGA) estimates the cost to comply with the EU’s serialization regulations as: Printing and serialization around US \$331,000 to \$397,000 (approximately €303,000 to €364,000) per packaging line; Anti-tampering around US \$199,000 to \$265,000 (approximately €183,000 to €243,000) per packaging line, and Verification with repository information systems around \$53 million (approximately €49,000,000) per year [24]. For a rough estimate of the equipment and software costs involved in a traceability implementation in developing countries requires in average \$126,000 USD ranging from (\$76,000-176,000). This cost doesn’t include GS1 registration, engineering costs required for hardware installation, training and education, downtime, Annual GS1 licensing fee and maintenance (Table 4) [23,25].

**Table 4:** From GS1’s “Regulatory Roadmap: Traceability of Medicinal Products”, an example of capital investment costs for a traceability implementation

Typical Track and Trace Solution in Emerging Markets				
Type	Capital	Item	Quantity	Costs (\$)
Hardware	Serialization print and verity	Serialization print and verity equipment	1	\$ 13,000- \$ 17,000
	Tamper evidence	Tamper evidence module	1	\$ 28,000- \$ 50,000
	Warehouse Station	Rework station	1	\$ 7,000- \$ 17,000
	Quality assessment station	Rework station	1	\$ 7,000- \$ 17,000
Software	Plant software	License	1	\$ 15,000- \$ 50,000
	Line software	Included in the equipment prices	1	\$0
	Integration to internal communication systems	If necessary	1	\$ 6,000- \$ 25,000
Total				\$ 76,000- \$ 176,000



**Technical:** Packaging/Label standards; IT connectivity and Expertise and Resource Availability

Manufacturers will require additional investment in systems and technology to meet emerging mandates for product identification, labeling, and data exchange. Systems will need to have the capability to generate, manage, and share key data elements, and interfaces will need to be developed to share that data with national traceability systems. The investment required will depend on the scope and requirements of the implementation. For example, the capabilities required to print and manage serialization data are much more sophisticated than those required for GTIN, batch/lot, and expiry date. Similarly, the capabilities required for printing directly on the pack are more advanced than those required to print and place a sticker label. Additional investments (e.g., barcode printers and scanners) will be necessary to print and test barcoded product labels [3,5,26].

### ***Isolation of Manufacturers in Low Resource Settings***

Failing to consider the needs of domestic manufacturers during the development of a global standards implementation timeline can put them at risk of non-compliance and reduce their ability to compete in the marketplace. In many cases, domestic manufacturers work with less capital and more manual processes than their global counterparts. As such, they may not be able to respond to new regulations and requirements with the same speed as multinational manufacturers. Domestic manufacturers may then fail to become compliant, which places their business at risk [23].

### ***Non-Standard Use of GS1 Standards***

Globally, there is consensus regarding which standards are needed to secure the supply chain namely, the inclusion of a product's GTIN, batch/lot, expiry, and serial number. However, there is a risk that countries, in their implementation, will fail to harmonize fully with this global consensus. For example, countries may seek to build in additional requirements beyond globally used standards. This deviation from the global use of GS1 standards effectively creates a parallel or proprietary requirement for a specific market, increasing both costs and lead times. When those additional requirements are country-specific, they can also hinder the manufacturer's ability to supply that product across borders [23].

### ***Developing Proprietary Solutions in Lieu of Adopting Global Standards***

Countries that require proprietary solutions as part of their traceability implementations may increase the cost of manufacturing and reduce flexibility in the ability of manufacturers to supply their markets. This can also pose a risk to commodity security, in particular for countries with relatively small markets, which run an increased risk of manufacturers withdrawing from commerce. Domestic manufacturers are disproportionately affected by proprietary solutions, which can pose significant technical challenges and hinder their capacity to supply to global markets [27].

### ***Scarcity of Expertise***

Implementation of global standards, processes, systems, and technology for traceability can be complex, especially around governance and management of master, transaction, serialization, and event data.

Manufacturers will develop new capabilities within their existing workforce and in some cases, hire additional experts for assistance during their transition. Thus education and capabilities development is imperative for before implementation of the GS1 standards [23,28-31].

## Conclusion

Aligning around a single set of global standards can support processes and capabilities that create value for all participants in a supply chain, from business partners down to the patients. A serialization investment can deliver numerous benefits for stakeholders including; Enhancing Supply chain data visibility; Increasing patient safety; Ensuring supply chain security and control; Increasing supply chain efficiencies and Improving trade and business across borders.

As track and trace system works with principle 'one size may not fit for all', it is important for countries to consider their priority areas and capacities to implement tracking and tracing system. Specially implementing global GS1 standard by domestic producers in LMICs should be evaluated carefully due to resource constraint, Lack of expertise, shortage of access to essential drugs, capacity of domestic producers to export their products and affordability of essential medicines.

Countries from LMIC settings should evaluate their capacity (technology adaptation of end users, expertise to install and maintain; financial capacity for start-up and annual licensing fees) and pilot the project if deemed necessary on priority areas before implementing the global standards in their immature industries. It is also important to understand that serialization is an investment in which software developers may urge the governments to establish this system for sake of promoting their business. Some of countries in Africa including Ethiopia are currently supported by USAID to start global GS1 standard in some program products like products used for HIV/AIDS and Malaria. It is better to think twice in such scenarios before scaling this program to other services, due to questionable sustainability of donor support and internal capacity to sustain the system.

In business there is always conspiracy of developing virus and anti-virus programs. Smugglers and counterfeiters have capacity to challenge any system (both technically and financially) in any society; Therefore, it is worth to improve the countries border control and national drug quality control laboratory capacity with advanced equipments to deal with this complex problem.

Finally, serialization is not ultimate solution for supply chain security and product safety and developing countries should empower their regulatory system for their domestic production and designing their own supply chain visibility system to address the imported products based on their own capacity than struggling with global serialization system is imperative.

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