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Pharmaceutical Serialization : A Challenge for Small Manufacturers

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ABSTRACT

The purpose of this paper is to focus on the Challenges faced by Small Manufacturers due to the Serialization compliance. Pharmaceutical serialization is the process of assigning unique serial number to each saleable product pack. Each product pack contains information about product source, Global Trade Identification Number (GTIN), Batch number, Expiry date and unique serial number. Pharmaceutical serialization is not new compliance, and it was initially introduced by Turkey in 2010, and other market such as the China and South Korea. Since many years China made compulsory for all supply chain partners to record drug distribution information of individuals drugs units in a traceability system.

As we are approaching to 2023, It will be final phase of 10 yearlong implementation of Drug Supply Chain Security Act (DSCSA) since compliance enacted in 2013. Verification router services (Saleable Return) is another compliance which was scheduled to enforce on 2020 but it is now push back to 2023 due to Covid-19 impact. Under 2023 DSCSA Act, manufacturers need to provide product tracing information in secure and interoperable manner electronically to distributors and wholesaler in supply chain. Wholesaler must transfer product tracing information to dispensers and pharmacy and verify saleable returns receive from supply chain stakeholders. Dispenser/Pharmacy should be able to receive Electronic Product Code Information Services (EPCIS) and product tracing information electronically and to be able to reconcile physical product unique identifier with electronic records. Finally, everyone in supply chain must be connected electronically through interoperable network which will allow regulatory bodies to track and trace the information's.

The importance of drug traceability has been increasingly emphasized and mandated by several countries across the world. The Drug Supply Chain Security Act (DSCSA) has been working on a pilot project with big pharmaceutical companies, wholesalers and distributors to design and test interoperable network to trace pharmaceutical prescribed drug electronically at package level. This will help supply chain stakeholders to verify the authenticity

of drug in United States.

Keywords : Drug Traceability, Pharmaceutical Serialization, Small Pharmaceutical Business, Technical Infrastructure, Digital Drug Traceability, Track and Trace System, EPCIS, Covid-19 Economic Impact, Customized Traceability System, Labelling System for Drug Serialization, DSCSA.

I. INTRODUCTION

Pharmaceuticals Serialization is an effective way to digitally trace the pharmaceuticals prescribed drugs and mitigating the risk of counterfeit drugs in the supply chain. The criminals, Illicit or counterfeit drugs smugglers divert fake medicine into the supply chain for maximize their profit. Counterfeit drugs are potential threat to public life and many countries and regulatory agencies are trying to enforce stringent law for stopping counterfeit drugs into the supply chain. Manufacturers, wholesalers, or distributors are initiated to implement blockchain based technologies to track their product digitally. Security is the reason for which blockchain is stated as most suitable for pharma supply chain as it prevents any entity from manipulating data. [2] Current globalization and trade regulations making it difficult to regulate pharmaceutical products. Criminals and illicit product manufacturers divert products from different countries to other destination countries where regulation is not so stringent to detect counterfeit drugs. Sometimes, criminals and drug counterfeiters use shell offshore companies and illegal bank accounts to facilitate the sale of falsified medicines.[3]

Evolution of technologies and increased globalization of pharmaceuticals trade benefited global healthcare industries. Now people have greater accessibility of critical medicine and can buy them from trusted source.[4] It is also giving an opportunity to counterfeiters and illegal drug traders to sell medicine through social media platforms and dark-web sites. There are multiple factors which attract people towards online medicine purchase such as geographical limitations, lower cost, fast go-to-market time, target direct customers, and wider reachability to customers. [5]

II. SMALL MANUFACTURER - LIMITED INFRASTRUCTURE AND PRODUCTION CAPABILITIES

Small Pharmaceutical companies generally does not have investment capabilities to establish large production units. They are more focused on manufacturing and circulation of specific branded or generic medicine target customer or specific disease control. Small manufacturers do face some major challenges in the supply chain due to poor infrastructure and lack of funds for research and infrastructure improvements. Existing pharmaceutical units are struggling to meeting global standards due to need of heavy investments in new production and packaging machineries. Digital pharmaceutical products traceability provisions require additional space in manufacturing units for specialized packaging equipment's to print the unique identifier in all packaging levels, label grading systems, barcode printer and vision systems. This setup needs huge financial investment for manufacturers and might be a good portion of their financial capabilities. Investing on serialization equipment's, label software, and digital traceability system make completely unbalance financial status of small pharmaceutical manufacturer. The cost basically involves the configuring of traceability system, various testing, validation and

deploying EPCIS software to integrate with internal packaging lines, Enterprise, and warehouse systems, synchronizing various master data. The cost also associates variably based on considering have pre-built, out-of-the-box integrations with organizations ERP systems. Wholesaler and dispenser also need to invest on drug scanner and specialized software which must connect to centralized database for verification. Since small manufacturers does not have sufficient infrastructure so implementing digital drug traceability is a question.

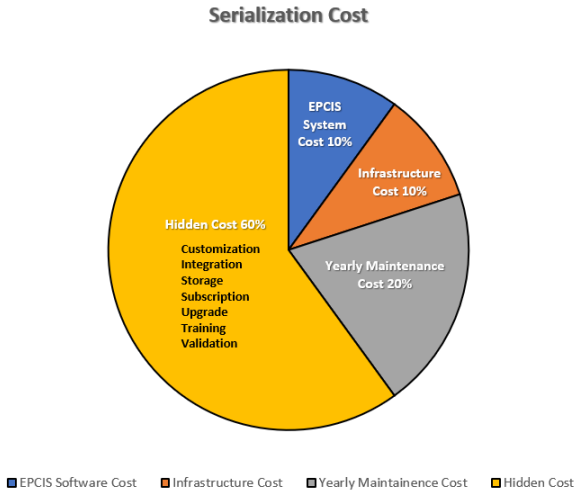

Figure 1. Serialization Implementation and Sustainability Cost

As per estimate the cost of adding packaging equipment's and infrastructure to support on-site or private service for data storage, processing, and access will increase production expense. Manufacturers information processing requirements will be 15,000 times more and the size of the serialization database and will be 5,500 times larger for the same volume of products manufacturer ship before implementing serialization process. Manufacturer will need database and application server licenses just to run your serialization solution, with additional costs for replicating in dedicated development, QA, and production environments, plus a separate high-performing environment for security, redundancy, and disaster recovery.

To compliant with serialization regulations, small manufacturer has to invest significant amount in computers, vision systems, barcode grading system, effective quality control to regulate country compliance. Some processes like detecting and discarding misprinted drug package in packaging line required AI based applications to optimize and improve manufacturing defects and reduce to minimum human interventions.[6]

These effective techniques are essential for pharmaceutical industry to control medicine manufacturing process as per (GMP). Existing packaging line and vision system are not capable to handle and digitally trace serialized drug as per regulatory compliance. The data integrity and capability of handling huge digital database must be compliant with: Attributable, Legible, non-editable, accurate and contemporaneous.[7]

A way to mitigate the risk of non-compliant with regulation is to invest in equipment which increase the already high production cost due to Covid-19 and market inflation (increase 80% cost of the end-to-end process)[8]

As per Good Manufacturing Practices (GMP), any system which works on GMP data such as product labels and batches must perform complete validation. Huge costs involve for validating serialization equipment's, Track and Trace software, integrations connection with serialization service provider, including all installation qualification (IQ) and operational qualification (OQ) documents to ensure systems are performing as per compliance. System and process validation requires continuous maintenance and testing of system upgrade, partner connections, and other compliance reporting for government each time serialization solution is updated. Since trade partners requirements are rapidly evolving due changes in regulatory requirements and new compliance enforcement so upgrade in serialization

system is necessary on regular basis. These upgrade many efforts from different departments for validating changes and analysis the impact of upgrade in other processes. [9] However, many small manufacturers also have realized that they must to invest on their infrastructure and it will benefit them as Return on Investment (ROI) on longer run. Their infrastructure and technical platform can streamline their process in various way including, big data collection, sharing on real time basis and trial results.[10] Sometime small pharmaceutical manufacturer looks into alternative option to avoid heavy investment on infrastructure improvements and setup. They delegate manufacturing authorization to Contract Manufacturing Organization (CMO) facilities as they have complete infrastructure setup to compliant with serialization requirements. In developing countries like India, small manufacturer doesn't hire specialized pharmaceutical consultants due to higher consulting fees and ultimately cost impact to finished and final drugs.[11] In many cases, big pharmaceutical manufacturer come into an agreement with hospitals to dispense their own branded medicine. Despite of heavy investment in infrastructure to adopt serialization compliance, these arrangements and agreements force small manufacturers to look into other segment of market and resulted reduction of earned revenue.[12]

These additional upgrade cost small manufacturer must spend every time whenever upgrade required. While serialization is necessary to mitigate the risk of counterfeit and illicit drugs in the supply chain, it will require a sizable capital investment to cover start-up expenses for packaging serialized drugs. This includes buying new packaging lines, label printing machines, vision systems, label grader, updating existing hardware and software, and training the staff. These expenses have significant impact on cost but it is also necessary to ensure proper efficiency and follow a compliant serialization process. [13] Other side It is also consider that these investment on improving technical infrastructure will be beneficial for pharmaceutical industries in longer run.

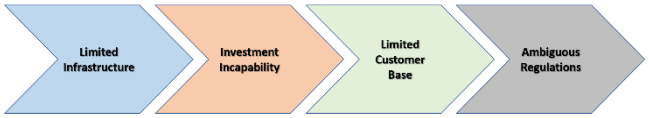

Figure 2. Pharmaceutical Serialization: Challenges for Small Business.

III. SMALL MANUFACTURER – INVESTMENT INCAPABILITIES

Small pharmaceutical companies produce specialty medicines to treat specific dieses. Due to limited numbers of customers and brand medicines, there revenue generation is very limited to specific products only. The drug digital traceability and serialization require a good amount of investment as it involves Traceability system, packaging line equipment, label control and warehouse rework systems. Small pharmaceutical companies generally have very limited allocated budget for additional setup of any machineries or software. Any further expense on technology or equipment's massively impacts their financial capabilities. Small medium pharmaceuticals manufacturing companies does not see any return on investment (ROI) as pharmaceutical serialization is regulatory compliance, but they admit serialization adoptability increase product quality assurance and mitigate the risk of counterfeit drugs. Even though there are many benefits of serializing drugs, and it is part of regulatory compliance, but it impacts tremendously to small pharmaceutical manufacturers. Initially many global or country specific regulatory meetings, small medium pharmaceutical business raised their incapability to adopt pharmaceutical serialization compliance.

IV. SMALL MANUFACTURER – LIMITED CUSTOMER BASE

Most small pharmaceutical manufacturers are producing limited products for specific or seasonal dieses. Their customer base is also particularly group of people which needs specialty treatment. The Year-on-Year Revenue growth of these pharmaceutical companies are very slow and depends on detectability of dieses and competitor in market. Some small pharmaceutical manufacturers produce drugs demanded on seasonal basis. In USA, demand of allergic medicine raises high on spring and summer season due to pollen, dust and insects. These manufacturers generate revenue due to seasonal demand or higher detection of dieses on population.

The manufacturing quantities of per batch are also very limited due to seasonal demand or customer specific drug requirements. Ultimately huge investment on serialization adoptability and implementation will increase production cost and force small manufacturer to increase product price. If small pharmaceutical manufacturer acts as contract manufacturer, then the cost of system integration will also occur connecting with each Brand Owner in order to exchange serialization data digitally with them. Digital serialization data exchange as per regulatory requirement incurred one of the biggest serialization costs in terms of both time and expense. Setting up single end to end connectivity requires considerable expense to serialization project and it could take minimum 30 days and costs $15,000 per connection, with the average CMO integration. In addition, each time a trade partner or government makes a change in their requirements, small manufacturer will need to make costly updates to sustain serialization process and meet regulatory requirements.

V. IMPACT ON PRODUCT COSTING AND PRICING

Serialization requires trading partners to exchange drug product tracing information when they take ownership of drugs, resulting in a tracing record that FDA and others can use to investigate suspect and illegitimate drugs. Under this DSCSA act, wholesale distributors must have traceability systems to verify the product identifier, information on each sealed homogeneous case of saleable returned product to wholesalers. A saleable returned product may not be further distributed by wholesaler/distributor until the product identifier is verified. The product should be managed as suspect product and keep as quarantine stock if the product identifier is not successfully verified. [14] Implementing all serialization provision need huge investment to setup additional packaging equipment's, labelling software and EPCIS System. This investment directly impacts product manufacturing cost and drug producers increase their sales price to recover additional product costing. Small pharmaceutical manufacturers approaching serialization, regardless of their size, revenue, and brand ownership, will rank price as one of their top decision criteria. But when it comes to developing an accurate serialization budget, many create their forecast without a thorough breakdown of all costs small manufacturers incur throughout the serialization life cycle and it will increase the product pricing.

VI. SERIALIZATION MAINTAINENCE AND SUSTAINABILITY COST

After serialization adaptation and process implementation, sustainability is another major challenge for small manufacturers. Serialization system and service provider charges for track and trace software that may occur as a one-time fee, or as recurring monthly or annual fees. These fees may cover a range of users or require individual licenses for each user or charges based on serial numbers

commissioned for pharmaceutical products. Companies may also meet additional storage and application server fees for system sustainability or system maintenance on cloud. Manufacturer needs to pay for the long-term database storage and system accessibility needed to meet regulatory and compliance related data-retention requirements. The infrastructure and system architecture must be able to support billions of unique identifiers generated by serialization system in its process each year. The entire database must be secure and easily accessible for authorized business partners for product traceability and authentications. There are often government data retention requirements for up to 12 years and same serial number should not reuse until 2 years after batch expiration or 5 years after batch manufacturing, whichever is later. Maintaining systems, database, and infrastructure incurred recurring cost each year which is an additional burden on small manufacturers who has limited, seasonal or patient centric product. This leaves in no other option for manufacturers but to increase product price.

VII. CONCLUSION

Implementing drug traceability system is necessary for stopping counterfeit and illicit drugs but small manufacturers are facing key challenges such as insufficient funds for infrastructure improvement, unavailability of secure technology and incapability to adopt and invest on drug traceability system. They also face other challenge such as grappling with structural vulnerabilities such as persistent social and economic inequalities, conflict and forced displacement, ambiguous regulations, and environmental fragility. Small manufacturers generally incapable for investing huge amounts of fund to establish serialization packaging line and Track and Trace Systems. The other critical cost of clinical trials/studies conducted over a longer period is a well-known challenge to small pharmaceutical companies.[15] Many big pharmaceutical companies can afford to hire resources to manage with financial budget of serialization requirements whereas smaller manufacturer may have budget constraint and more challenges to implement compliance.[16]

In 2018 Tracelink conducted an survey and found that only 8% of pharmaceutical manufacturers have established integration for serialization process with their contract manufacturer (CMO) and only 11% CMO was ready with serialization infrastructure to ship product.[17]

Small manufacturer can adopt some best practices to mitigate the risk of being non-compliant as per regulations. They can modify or enhance their existing Base ERP system and design in-house serialization process as scale of producing serializing product volume is small. It can also incorporate additional database capacity requirement in existing ERP due to limited serialized product and volume. Sustainability of in-build serialization program will be very low and can be include with existing ERP support. For label designing and printing, they can adopt cost effective small software such as Bartender as their running cost and license are low. Some country requires regulatory reporting requirements so additional webservices or API can be developed to integrate with customers or regulatory portals. All these options are only viable if small manufacturers are producing small scale of batch quantities and does not need complex regulatory reporting requirements such as Russia. If manufacturer is producing dieses specific medicine or their target customers are doctors and clinics, then they are exempt for sending some transaction information. Government and small pharmaceutical manufacturer must collaborate and discuss such existing costing issue as it may increase drug production cost and ultimately impact to medicine selling price to consumers. New drug serialization and traceability mechanisms were evaluated at the joint initiative of drug manufacturers, wholesale distributors and community pharmacists.

Pharmaceutical industry is further trying to adopt new secure technologies like block chain in interoperable digital communications. [18]

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