The impact of Serialisation on operational efficiency and productivity in Pharmaceutical sites: A Literature Review

Daniel O' Mahony

College of Science & Engineering, University of Galway, Galway, Ireland/Faculty of Science, Griffith College, Dublin

Olivia McDermott

College of Science & Engineering, University of Galway, Galway, Ireland

Alan Lynch

Faculty of Science, Griffith College, Dublin

Kathryn Cormican

Enterprise Research Centre and LERO - the Irish Software Research Centre, School of Engineering, University of Galway, Ireland

Abstract

Serialization technology was introduced to protect the pharmaceutical supply chain from falsified and substandard medicines infiltration. The implementation of serialization systems required a substantial investment by pharmaceutical manufacturers. This study investigated the impact of Serialisation on operational efficiency and productivity in the pharmaceutical Industry. A literature review demonstrated limited publications on Serialisation concerning its costs and effects on packing line operational efficiency and productivity. Therefore, a literature review was carried out to assess the relationship between Serialisation, operational efficiency, and productivity. The study revealed that Serialisation had the potential to impact pack line Operational Equipment Effectiveness negatively and line availability, as well as the unit cost of packaged pharmaceuticals and that actual capital costs of Serialisation were greater than the costs originally outlined by policymakers. In addition, the study identified a trend where pharmaceutical sites move away from smaller batch production and toward larger batches to gain greater efficiencies. This is the first study of Serialisation literature from a manufacturing viewpoint.

Keywords: Pharmaceutical Cost of Goods Sold, Pharmaceutical COGS, Pharmaceutical O.E.E., Serialisation O.E.E.

1. Introduction

Since the 1980s, the World Health Organization (WHO) has identified a growing threat to patient safety from falsified and substandard medicines. These fake medicines had started to gain a foothold in the legitimate supply chain (World Health Organisation, 2023). As a result, there were multiple incidents where unsuspecting patients were given unsafe medicines resulting in injury and death. By the late 1990s, the reported incidents of falsified medicines started to rise dramatically, and Regulatory authorities started to take action to protect patients (Buckley *et al.*, 2013). The pharmaceutical Industry also realized the danger posed by criminals operating in their Industry (International Federation of Pharmaceutical Manufacturers and Associations, 2023). The risk to patient safety, reputational damage and

revenue loss focused the Pharmaceutical Industry's attention on counterfeit medicines(OECD/EUIPO, 2020).

Implementing anti-counterfeiting regulations has required a large pharmaceutical industry investment in new equipment and resources (Chatterjee, 2014). The regulations introduced to protect pharmaceutical supply chains use serialization technology to print a unique identifier on each medicine pack. Every carton, bottle or medicine vial produced for the U.S. and European markets must carry a serialized code unique to that pack. The serial code, expiry date and batch number are contained in a 2D matrix code mandated in regulations, with serial codes decommissioned at the point of dispensing by a pharmacist (European Medicines Verification System, 2023). Printing and checking a 2D Matrix code is simple, but flawlessly printing 200 codes per minute on a 24/7 cycle shift in a pharmaceutical manufacturing facility requires great skill and resources (O'Mahony, 2020). In addition, unit-level Serialization creates a large amount of data that must be stored, retrieved, and communicated across multiple systems. For example, a large pharmaceutical company will produce 650 GB of serialization data annually (Willis, 2017). Any mismanagement of this data can lead to production line stoppages, product recalls and a halt to the supply of essential medicines to patients (Sarkar, 2022).

This research aims to assess the impact of Serialisation on the efficiency and productivity of pharmaceutical sites from the literature viewpoint. The next objective was to quantify the impact of Serialisation on pharmaceutical facilities' operational efficiencies using measurements such as Operational Equipment Effectiveness (O.E.E.) and production line availability measures. Serialization inherently requires adding new process steps into existing operations which might infer a reduction in O.E.E. (ARSLAN, 2019; Sarkar, 2022). Conversely, adding new equipment might increase O.E.E. levels as when replacing existing equipment, the O.E.E. can increase due to more modern technology and higher equipment speeds resulting in less downtime or minimizing product quality issues (Penfold, 2018). The research looked at the literature to gain insight into the experiences of manufacturers in the post-serialization era.

The last objective was to determine if serialization processes impacted site productivity. Serialization required a substantial pharmaceutical industry investment in capital expenditure (O'Mahony, 2020; Sarkar, 2022). New expertise and resources were required to manage and

operate the serialization system and to store and distribute data(Cordon *et al.*, 2016). Serialization track and trace systems can aid productivity by providing manufacturers with better data to manage supply chains, and productivity changes can be measured using changes to the cost of goods sold (COGS) and unit pricing (Cordon *et al.*, 2016; ARSLAN, 2019). Serialization and the trend toward operational excellence techniques have coincided to create a greater impact on productivity(Jablonski and Brochu, 2006). There is a trend toward moving away from smaller batch sizes which may have coincided with the implementation of serialization processes, and these two changes in the production process have exacerbated each other (O'Mahony, 2020)

The purpose of the literature review was to:

(i) Identify what consideration, if policymakers and industry bodies gave any, as to the impact of Serialisation on operational efficiency in the pre-serialization phase and the period after the implementation of serialization processes.

(ii) Identify from the literature the impact of Serialisation on operational efficiency and pharmaceutical site productivity.

Section 2 outlines the literature related to Serialisation and its origins, the requirement for Serialisation and the regulatory requirements around Serialisation. Section 3 outlines the methodology. Sections 4 and 5 present the results and discussion, while Section 6 outlines the conclusion.

2. Serialization and its Origins

2.1 Counterfeit medicines

Estimations vary on the value of trade in counterfeit medicines. However, there is consensus that sub-standard and falsified medicines present an enormous risk to patient safety and the legitimate medicines supply chain (European Commission, 2008). It can be difficult to assess the scale of the black market in counterfeit drugs. By its very nature, the trade in illicit medicines is controlled by criminals and can be dangerous to investigate. In addition, drug companies may be aware of copies of their medicines in some markets but may be slow to discuss these findings publicly (Cockburn et al., 2005).

Pharmaceutical supply chains are complex and stretch globally (Singh *et al.*, 2016). For example, a pharmaceutical company may fill semi-finished products into primary packaging at their facilities but may have an outsourced contract packaging organization (C.P.O.) manage the packing of drugs into labelled secondary packaging. Finished products may then go to an in-house distribution centre or may instead go to a licensed third-party logistics provider (3PL) or a licensed wholesaler/distributor. The complexity of the pharmaceutical supply chain makes it susceptible to infiltration in terms of sub-standard raw materials and fake finished products, according to a WHO report on counterfeit medicines (Pisani, 2017). Adopting serialization systems is just one of the tools used to combat illegal medicine supply (Hall, 2012).

2.2 Examples of falsified medicines in the supply chain

Heparin is a blood-thinning drug used to treat dialysis patients and seriously ill post-operative patients to prevent blood clotting. In 2008 fake versions of Heparin started to appear in the U.S. market. The active pharmaceutical ingredient in Heparin was switched for a cheaper chemical compound with anti-coagulant properties (Hubbard, 2009). Infections caused by injections of fake Heparin caused the death of 81 patients in the U.S. (Harris and Bogdanich, 2008). There were also reports of infections from the counterfeit Heparin in the E.U., though these did not result in any deaths (European Medicines Agency, 2018)

In 2012 reports emerged of counterfeit Avastin circulating in the U.S. market. Avastin (Bevacizumab) is a drug developed by Roche and Genentech as an oncology medicine for treating tumours and had sales of $6bn USD in 2012 at a product cost of about $2,500 per dose. When U.S. regulators tested the fake Avastin, they found no active pharmaceutical ingredients (Mackey *et al.*, 2015). There are multiple examples of counterfeit medicines and adverse side effects (WHO, 2003; WHO, 2013; IRACM and Przyswa, 2013).

In 2007 over 4 million articles of counterfeit medicines were seized by customs officials (European Commission, 2008). By 2011, this number had increased over 5-fold to 27.4m articles of medicine with a retail value of €27.6m (European Commission, 2012). At the time of policy formation regarding falsified medicines and Serialisation, the threat of unlicensed drugs grew alarmingly. However, by 2019 the figures had dropped, with 166,000 articles seized with a retail value of just over €4m (European Commission, 2019). In addition, EUROPOL's MISMED program, a crackdown by law enforcement, customs and health

regulatory authorities from 16 countries in Europe, netted a haul of more than 13 million doses in excess of €165 million (Europol, 2020).

The European Union allows the free movement of goods and intra-national trade within the community. Medicines are often legally relabelled for sale in different member-state markets. Parallel market relabelling operations may also take medicines from outside the E.U. for remarketing in another E.U. member State(Bird and Chaudhry, 2009). While this free movement of goods is accepted, the activity is seen as susceptible to criminal infiltration or abuse (Vander Beken and Balcaen, 2006). The European falsified medicines directive demands specific measures, including Serialisation, to control parallel trade. In the U.S., parallel trade is also a susceptible entry point for illegal medicines into the supply chain (Liang, 2006).

The European Union Intellectual Property Organisation (EUIPO) has worked with the Organization for Economic Cooperation and Development (OECD) to offer a deep analysis of the impact of counterfeit medicines in the European Union. In a 2020 report, the EUIPO and OECD used a figure of €4.4bn for the global trade in counterfeit medicines. The report outlines that 38% of seized counterfeit medicines infringe U.S. patent and trademark rights. European trademark and patent holders are the next most affected group (EUIPO and OECD, 2020).

Another 2019 EUIPO report estimates the indirect impact of counterfeit medicines on the European pharmaceutical Industry. The report calculates that unlicensed medicines cost 37,700 jobs in the E.U. In addition, another 53,000 jobs are lost in supporting activities. The statement sizes the cost of counterfeit medicines at €10.2bn per annum when lost revenue is considered (EUIPO and OECD, 2019).

The Pharmaceutical Security Institute (P.S.I.) gathers incident data privately from pharmaceutical companies where their products have been counterfeited but may not wish to highlight these incidents publicly. The P.S.I. reported 5,987 pharmaceutical crime incidents in 2021, increasing by thirty-eight per cent (+38%) from the previous year (Pharmaceutical Security Institute, 2023). The increase in new incidents can be attributed to easing pandemic restrictions and criminal organizations taking advantage of new opportunities.

3. Methodology for Literature Review

A literature review supported the main aim of the research to determine the impact of Serialisation on operational efficiency and productivity on pharmaceutical sites. The literature review sought to identify relevant journal articles, industry reports and other sources that could inform the key objectives of the research. While many literature reviews excuse grey literature, this paper did not. Grey literature is defined as: "*that which is produced on all levels of government, academics, business and industry in print and electronic formats, but which is not controlled by commercial publishers"* (Pappas and Williams, 2011; Mahood *et al.*, 2014; Bellefontaine and Lee, 2014). There were several reasons for the inclusion of grey literature. One reason is that grey literature can broaden the scope to more relevant studies, providing a complete view of available evidence(Mahood *et al.*, 2014). Also, there can be a delay between research and publication, and thus access to innovative and up-to-date information and reports is more challenging (Pappas and Williams, 2011)

The literature review was conducted in two phases. The first phase of the literature review examined how policymakers and industry stakeholders considered the impact of serialization processes on operational efficiency and productivity. The themes of policymakers and industry bodies considering efficiency and productivity during the formulation of serialization regulations and its impact in the post-serialization period were analyzed. Also, it examined how operational efficiency is measured in the pharmaceutical Industry. A search was conducted to find articles on how the pharmaceutical Industry adopted serialization technology and if serialization systems had hindered or helped efficiency. This section also sought contributions about line availability.

The final section of the literature review focused on productivity. The review examined how productivity is measured in the pharmaceutical Industry. Contributions to the cost of goods sold and unit cost were examined. The literature review sought to examine articles on the relationship between serialization and unit cost.

Table 1: Literature review strategy

Literature Review Strategy		
Phase	**Topic**	**Sources**

Phase I	Measurement of operational efficiency in the pharmaceutical Industry and the impact of Serialisation	E.C. Reports, F.D.A. Reports, Industry journal articles and industry magazines, journal papers (peer-reviewed)
Phase II	Measurement of productivity in the pharmaceutical Industry and the impact of Serialisation on productivity in pharmaceutical packaging companies	E.C. Reports, F.D.A. Reports, Industry journal articles and industry magazines, peer-reviewed journal papers

Search tools used in the literature review included Sage Journals, EBSCO, Google Scholar, ResearchGate, PubMed, EOLAS, Emerald Insight and J-Stor. The literature review used a combination of Boolean Search functions, including the U.K. spelling of "serialization" and the U.S. spelling of "serialization". In addition, variations of "operational effectiveness", "O.E.E.", "Operational Excellence", "OPEX", and "impact" were used in the Boolean searches.

The authors carried out a thematic analysis aligned with the research objectives under four main themes: the costs of Serialisation, serialization effects on manufacturing efficiency, serialization effects on planned downtime productivity and equipment efficiency and overall pharmaceutical industry productivity.

4. Results

4.1 The Literature on Serialisation in Pharma

Much of the literature related to the topic of Serialisation in pharmaceuticals discusses the regulatory requirements for Serialisation (Nalam, 2023), the need for Serialization in counteracting drug counterfeiting(LAHJOUJI *et al.*, 2023) and the track and traceability aspects of Serialisation (Trajanovska *et al.*, 2023). However, apart from some reputable industry and consultants' reports (Bellm, 2015; Gyurjyan *et al.*, 2017; McKinsey, 2017), few studies address the costs of Serialisation, the impact of Serialisation on manufacturing in terms of productivity, line efficiency and continuous flow. The studies that do address manufacturing serialization are concerned with the storage of the data involved for the serialization information(Shanley, 2016; Nalam, 2023; Nguyen *et al.*, 2023) or the technology applied(Abdallah and Nizamuddin, 2023; Rajora, 2023; Trajanovska *et al.*, 2023).

4.2 The expected costs of Serialisation

The primary literature related to the expected costs of Serialisation within the European pharma industry was the European Federation of Pharmaceutical Industries and Associations (EFPIA) report in response to European Commission on the Falsified Medicine Directive. This report estimated the expected costs of implementing Serialisation in the pharmaceutical Industry of €125m annually for Serialisation (EFPIA, 2012). The EFPIA report also cites a cost of 1.6 cents per pack of medicine and an annual cost to a large manufacturer of €8m annually. In its submission, the EFPIA stated that an average manufacturer would have €7bn in sales and produce 500m packs of medicine per year (EFPIA, 2012).

The European Commission has published the correspondence from industry stakeholders, including submissions from Pfizer and Amgen which refer to the cost of Serialisation; however, none of the 100 submissions mentions an impact on the operational efficiency of manufacturing sites and, therefore, a potential impact on the availability of medicine (EUROPEAN COMMISSION Enterprise + Industry, 2008).

In the final European Commission's impact report on the falsified medicines directive, there is no reference to any possible impact on operational efficiencies. However, the report does estimate that once-off costs for serialization technology would come to €150,000 per pack line. This estimated that across the 12,000 non-prescription medicines pack lines, this would mean an industry investment of €1.8bn for line upgrades. In addition, another €4bn investment was required to provide the necessary I.T. systems to manage the flow of serialized data. The final report estimated that printing and packing serialized codes would cost 2 cents per pack in the first five years. With 14.85bn packs of prescription medicines traded annually in the E.U., 2 cents per pack equates to an industry cost of €297m per annum to print and check serialization codes on European pack lines (COMMISSION OF THE EUROPEAN COMMUNITIES, 2008b).

In the U.S., the F.D.A. did not directly carry out a similar impact report; however, several indirect reports did assess the potential impacts of serialization processes on the Industry. The Pew Healthcare Foundation published comprehensive research that estimated the costs of Serialisation (Pew Charitable Trusts and Booz Allen Hamilton, 2013). The Pew Healthcare

report, based on estimates from both pharma companies and vendors, set the average cost to serialize a pack line at $1.4m. This cost includes not just the cost of equipment and software but also the cost to implement the project and enterprise costs. This was a multiple of the European Commission's estimates and highlights additional labour costs of $291,000 per annum per pack line(Pew Foundation and Booz Allen Hamilton, 2014). There is no reference to an impact on operational efficiency in the report. The report stated that no public analysis was available on the costs associated with implementing Serialisation at the time of publication.

The U.S. Center for Disease Control (C.D.C.) and Deloitte consultants did publish an impact assessment report on 2D data matrix code printing on the vaccine supply chain(Deloitte, 2012). The report considered the impact of Serialisation on manufacturers, distributors and healthcare providers (Robinson *et al.*, 2013). The report cited the complexity of printing 2D matrix codes compared to traditional linear barcodes as regulations stipulated that manufacturers achieve a minimum ISO grade C for printed labels. In addition, each label must be checked to ensure its readability. Barcode scanners are too slow to read all the labels on a high-speed pack line, and therefore industrial grade cameras are used, adding more complexity and cost. Along with the complexity of the 2D codes, the F.D.A. stipulated that manufacturers would still be expected to print linear barcodes on the packaging, thus increasing the risk of printing errors (Center for Drug Evaluation and Research, 2018). Again, the C.D.C. impact report did not reference Serialisation's potential impact on operational efficiency.

4.3 Serialization Effects on Manufacturing Efficiency

In manufacturing environments, operational efficiency is often measured using the O.E.E. method (Overall Equipment Effectiveness). The O.E.E. concept was first introduced by Seiichi Nakajima in the seminal work Total Productive Maintenance (TPM), published in 1988 (Nakajima, 1988). Nakajima identified six factors that had the most impact on O.E.E. These are the big losses, Equipment failure/breakdown losses, Setup/adjustment time, Idling and minor stop losses, Reduced line speed, and Reduced yield until machines stabilize and quality.

The O.E.E. calculation provides a common standard to determine production efficiency in different manufacturing sites and industrial sectors (de Ron and Rooda, 2006). O.E.E. is made up of three elements (i) Performance, (ii) availability (iii) quality. Performance is a

measurement of line speed. For example, a packaging machine rated to produce 200 packs per minute but that only produces 100 packs is operating at 50% performance. Availability is a measure of time. The percentage of stoppage time during which a pack line should be available for packing processes. Quality measures the percentage of good quality products produced from the total. The O.E.E. is calculated as a composite of all three measurements.

OEE % = % Performance X % Availability X % Quality

Serialization can affect the three measures that comprise the O.E.E. calculation(Cordon *et al.*, 2016; ARSLAN, 2019). The regulations promote using ISO standards that measure the quality of the 2D data matrix codes on the medicine pack (ISO, 2006). The requirement to print complex 2D matrix codes, apply tamper evidence seals and check the readability of print may slow the pack line speed performance. In addition, line availability may be affected by the time operators set up serialization data and clear down unused serialized codes and stoppages caused by poor-quality print(Ramesh, 2015; Fortier and Joevan, 2017).

While there was an absence of comments on pack line efficiency in the impact reports by the C.D.C. and the European Commission, there was some industry realization of the potential of a negative impact on O.E.E. Rotunno *et al.* (2014a) commented that due to the changes in the process operations due to serialization activity, there could be an impact to the overall equipment effectiveness (O.E.E.) of the pharma production lines. Waiting for continuous data exchanges and data valid signals may result in an overall reduction in line speeds and a reduction in performance efficiency" (Rotunno *et al.*, 2014b). A report from Pharma Logistics I.Q. (2017) also cited efficiency-related costs, which were also unquantified.

In a report, Healthcare Packaging (2015) estimated the negative O.E.E. impact at 8% to 10% post-implementation. They estimated that O.E.E. would recover to a point 4% lower than pre-serialization (Rodgers, 2014). This range of O.E.E. loss was validated in an article in Pharmaceutical Commerce magazine, where a loss of between 5% and 10% was estimated for the period after ramp-up and stabilization, but losses of up to 30% were observed during the ramp-up period after implementation (Ozkaya *et al.*, 2017). The article also pointed out that operators need training and experience to maximize efficiency post-serialization. The International Society of Pharmaceutical Engineers (ISPE) indicated 10% to 25% losses for up to 2 months post-serialization implementation. Penfold (2018) states that lines may recover

to 1% to 5% lower than the original O.E.E. position after about six months (Penfold, 2018). However, these calculations are estimated based on a combination of the Healthcare Packaging study (Rodgers, 2014), personal experience and input from industry colleagues. Due to the emerging nature of the technology, there was not a large amount of supporting literature for the O.E.E. impact claims in the ISPE study.

One of the advantages of the 2D Matrix Codes (D.M.C.) used for Serialisation is that they are flexible from an operational perspective, as the D.M.C. is readable from any orientation. In addition, the codes have built-in error correction that allows a printed code with up to 30% degradation in print quality to be effectively still read. From an O.E.E. quality factor perspective, the 2D data matrix codes help maximize O.E.E. (GS1 AISBL, 2013).

4.4 Planned downtime productivity and Equipment Efficiency

The Harvard Business Review defines productivity as "the number of labor hours required to accomplish a given task compared with the standard in that industry or setting." A productivity gain is when a manufacturing site produces more with the same resources than peer companies, i.e. doing more with the same resources. On the other hand, the same publication defines efficiency as “doing the same with less. Companies most often improve labour efficiency by finding ways to reduce the number of labor hours required to produce the same level of output” (Mankins, 2017). The serialization implementation process is not a single event, as software and hardware must evolve to meet regulatory and market requirements. As regulations evolve, so must the software and hardware on packaging lines(Fortier and Joevan, 2017; Ozkaya *et al.*, 2017).

Each time a serialization system is updated to meet these regulatory requirements, the packaging line must be stopped. These stoppages affect the productivity of the manufacturing site. Updates to serialization equipment are classified as planned maintenance and do not affect the availability measures in O.E.E. Even though these stoppages are planned, the effect on productivity should be measured. Reductions in productivity will be reflected in the cost of goods (COGS) from the site and in the price patients pay for healthcare(Gyurjyan *et al.*, 2017; McKinsey, 2022).

As serialization processes evolve with new regulatory demands, the time required to update and maintain systems is accounted for (Penfold, 2018). If pack lines become unavailable due to updates in pack line software and systems, this may not be captured in an O.E.E. measurement. Planned maintenance may be used in pharmaceutical sites to mask some of the productivity impacts caused by the requirement to update serialization equipment (O'Mahony, 2020).

4.5 The OPEX wave in Pharma

O.E.E., OEEM and *E* measurements are part of the operational excellence framework (OPEX)(Borges, 2023). The concepts associated with operational excellence grew from the methodologies adopted by Toyota and other Japanese manufacturers (Hayes and Wheelwright, 1984). The pharmaceutical Industry was a late starter in operational excellence (Chatterjee, 2014). This was evident in the high levels of raw materials and finished inventory carried by the pharmaceutical sector compared to other industries (Spector, 2018), (Starke and Kumar, 2013).

The branded pharmaceutical Industry enjoyed a high-margin environment until the introduction of the Hatch Watchman Act in 1984. This legislation paved the way for generic drug manufacturers to compete with branded drug companies once a medicine no longer had patent protection (MOSSINGHOFF, 1999). The squeeze on margins by generic manufacturers gave pharmaceutical companies a "burning platform" to initiate improvements (Schonberger, 2007). However, by the start of the 21st century, drug companies were starting to feel the pressure imposed on the Industry by generic medicines. Pharmaceutical companies found that their margins quickly eroded once drugs came off patent. As a result, manufacturers needed to adopt lean manufacturing techniques to compete in markets not protected by patents (Bellm, 2015).

The imposition of manufacturing licenses by regulators was often cited as a reason for pharmaceutical manufacturers not trying to improve their processes. Processes were seen as frozen and not open to improvement (Friedli *et al.*, 2013). In the mid-2000s, leading pharma companies started to adopt operational excellence programs. Examples include Genentech (Griffith *et al.*, 2010), Abbott Pharmaceuticals (Starke and Kumor, 2013) and Pfizer (Werani *et*

al., 2010). Following decades of focusing on quality control and stabilization programs for the control of manufacturing processes, pharma companies have moved to a new phase of trying to improve their organizations and processes systematically.

The pharmaceutical Industry's adoption of operational excellence techniques since the 2000s led to substantial improvement in O.E.E. and other key performances. A St. Gallen benchmarking report outlines the improvements in O.E.E. by the pharmaceutical company participants between 2006 and 2012 (Bellm, 2015). The report cites a 53% gain in O.E.E. performance. In 2007 the average O.E.E. in a best in class of food processing operation was 24% ahead of the average O.E.E. in a best-in-class pharmaceutical company. In a 2015 analysis of global " best in class" pharmaceutical sites, Ireland had 5% of the total (Bellm, 2015).

Part of the reason that pharmaceutical companies struggle with O.E.E. compared to other industry sectors is due to batch changeover times. Regulations oblige companies to fully clear down packing lines between batches (European Commission, 2017). Information regarding the batch number, expiry date and Serialization information must also be set up on the pack lines before manufacture, and each step of the process must be checked and double-checked against standard operating procedures (S.O.P.s). Best-in-class pharmaceutical companies achieved a four-fold reduction in changeover times compared to the poorest-performing sites (Pharma Manufacturing, 2007). However, just-in-time manufacturing and build-to-order batches mean an increase in the frequency of changeovers. More batch changeovers negatively impact line availability and O.E.E. (Casali, 2019). The serialization setup process can contribute directly to these changeover times.

Some of the negative impacts on O.E.E., identified in the literature and previously discussed, were exacerbated by this drive toward lean manufacturing and operational excellence. For example, any delay in setting up serialization information for a batch during batch changeover impacts availability(Borges, 2023). In addition, the more batches that go through a pack line, the greater the risk of the serialization label print and check systems causing errors and affecting product quality.

Negative impacts on O.E.E. must be balanced against some positive effects of serialization implementation. The age of the pack line may influence this balance. Pack line equipment generally has a lifecycle of 20 – 25 years (COMMISSION OF THE EUROPEAN COMMUNITIES,

2008a). With the onset of Serialisation, some manufacturers may have replaced older pack lines with newer equipment (Fortier and Joevan, 2017; GS1 Ireland, 2023). This capex investment in new equipment may also have brought better line speeds and faster changeover times. Adding better cameras and printers during serialization installation may improve line performance even without replacing older pack lines. One vendor reported that a manufacturer saved $100,000 USD annually by replacing manual inspectors with an automated vision system during a serialization implementation (Pirrera and Jordan, 2014). Another vendor reports that a client started to monitor O.E.E. post serialization seriously, and by working closely with operators, the business was able to eliminate waste and increase O.E.E. by 20% (Butschli, 2017).

The pharmaceutical pack line is the epitome of the late-stage customization demanded by lean manufacturing, as a medicine does not become a medicine until it is correctly labelled and serialized for a specific market. Therefore, any negative or positive impact on O.E.E. or OEEM will affect a manufacturing site's operational efficiency and productivity.

4.6 Pharmaceutical industry productivity

The St. Gallen studies outline the improvements in equipment efficiency in the pharmaceutical Industry over 10 years (Bellm, 2015). However, during this period, no real improvement in pharmaceutical industry productivity has occurred. A key indicator of a manufacturing company's progression in lean manufacturing is its inventory turns. Spector reported that compared to other manufacturing industries, the pharmaceutical sector made little impact on inventory levels from 2000 to 2009 (Spector, 2018). Analysis of public company data from 2007 to date indicates that inventory turn has essentially flatlined (Discover CI, 2020). McKinsey reports that the cost to produce medicines has not changed across the Industry, the generic medicines sector being the only exception(Gyurjyan *et al.*, 2017).

This stagnation in the cost of goods as a percentage of total sales across pharmaceutical productivity was also identified by Basu et al. during the period 2006 to 2008 (Basu *et al.*, 2008). Vernon *et al.* (2007) identified that the cost of goods in medicines manufacture relates directly to the cost of healthcare. Any reduction in the cost of goods is taken as an additional margin by manufacturers, while any increase in the cost of goods is passed on through higher prices. If serialization processes did affect productivity, this might be reflected in the cost of

goods and healthcare for patients. Serialization processes do not just impact the packaging areas in pharmaceutical companies. A study by GS1 Ireland and industry consultants Enterprise System Partners found that serialization project teams included representatives from departments such as packaging, automation, engineering, I.T., quality, operations, manufacturing, artwork, and sales (GS1 Ireland, 2023). The Harvard Business Review (H.B.R.) defines this cross-functional activity as "organizational drag". The H.B.R. reports that companies can lose up to 20% of their productive capacity through structures and processes that consume personnel's time (Mankins, 2017).

4.7 Conclusion

Sufficient gaps in the literature were identified to warrant the design of a research method to investigate the impacts of Serialisation on operational efficiency and productivity in the pharma manufacturing context. The literature provided some base data on the considerations of policymakers and industry representatives as to the expected capital and operational cost of Serialisation. However, there was little follow-up in the literature regarding the accuracy of the original expectations outlined in policy maker's impact assessment reports. No literature discussed a detailed impact of Serialisation on operational efficiency or productivity. The literature indicated that efficiency might increase or decrease because of Serialisation, but no clear outcomes were identified. Very little data was available in the literature that discussed Serialisation in the manufacturing context. The literature did not indicate how serialization processes might have affected pharmaceutical productivity or the cost of goods sold.

5. Discussion & Conclusion

This research aimed to determine the impact of Serialisation on operational efficiency and productivity on pharmaceutical sites. The research had two objectives, firstly, to test the assumptions made by industry bodies and policymakers before the implementation of Serialisation. Secondly, to assess the impact of Serialisation on operational efficiency and the impact of Serialisation on-site productivity.

As discussed in section 4.1, the literature is sparse about the productivity and efficiency impacts of Serialisation on Pharma and is not specific in terms of the costs of Serialisation. This study found that despite all types of studies related to Serialization aspects, for example, the reasons for Serializations, the benefits of serializations, the regulatory aspects of Serialisation and the data responsibilities that come with Serialisation that there is a dearth of studies related to the costs to manufacturers and other productivity effects on the supply chain.

The study has theoretical and managerial implications for the pharma industry. This is one of the first literature review studies on Serialisation effects on manufacturers in the pharma industry and can inform the Industry of the downstream effects and issues around Serialisation. The research and literature that was reviewed indicated that Serialisation has the potential to have a negative impact on operational efficiency in pharmaceutical sites. There was some postulation in the literature before implementing the Drug Supply Chain Security Act (DSCSA) and the European Falsified Medicines Directive (F.M.D.) that Serialisation could improve operational efficiency. There was an argument that new equipment and interconnected systems could improve operational effectiveness. O'Mahony (2020) found in a study of Irish Pharma manufacturers that costs had increased since serialization introduction and that Serialisation had an impact on productivity.

The research also looked back on the assessments of policymakers and industry bodies before the track and trace regulations. From the literature, it was clear that little consideration was given to the potential impact of Serialisation on efficiency and productivity. Estimations by policymakers on the cost on costs associated with Serialisation were also inadequate. This research indicated that policymakers underestimated the cost of serialization projects by a factor of four, as the 2008 European Commission Assessment report had predicted an average cost of Serialisation per pack of 5 cents (EUROPEAN COMMISSION Enterprise + Industry, 2008). Further research could be conducted to narrow down the annual cost of Serialisation in pharmaceutical sites as a follow-up to this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Bibliography

Abdallah, S. and Nizamuddin, N. (2023) 'Blockchain Based Solution for Pharma Supply Chain Industry'. *Computers & Industrial Engineering*, p. 108997.

ARSLAN, M.Y. (2019) 'Leveraging O.E.E. Tracker Tool to Address Efficiency Losses of Packaging Lines Resulting from Track & Trace Compliance in the Pharmaceutical Industry'.

Basu, P. *et al.* (2008) 'Analysis of Manufacturing Costs in Pharmaceutical Companies. *Journal of Pharmaceutical Innovation*, 3(1), pp. 30–40. DOI: 10.1007/s12247-008-9024-4.

Bellefontaine, S. and Lee, C. (2014) 'Between Black and White: Examining Grey Literature in Meta-Analyses of Psychological Research'. *JOURNAL OF CHILD AND FAMILY STUDIES*, 23(8), pp. 1378–1388. DOI: 10.1007/s10826-013-9795-1.

Bellm, D. (2015) *Operational Excellence in the Pharmaceutical Industry – An Architecture for Emerging Markets to Obtain the Title of Doctor of Philosophy in Management Submitted by Daniel Bellm from Germany Approved on the Application of Prof. Dr. Thomas Friedli and Prof. Dr. Wolfgang Stölzle Dissertation No. 4331 Difo-Druck GmbH, Bamberg 2015 The University of St.Gallen, School of Management, Economics, Law, Social Sciences and International Affairs Hereby Consents to the Printing of The*. St. Gallen University: University of St.Gallen, School of Management, Economics, Law, Social Sciences and International Affairs. Available at: https://www1.unisg.ch/www/edis.nsf/SysLkpByIdentifier/4331/$FILE/dis4331.pdf (Accessed: 22 June 2020).

Bird, R.C. and Chaudhry, P.E. (2009) 'Pharmaceuticals and the European Union: Managing Gray Markets in an Uncertain Legal Environment'. *Va. J. Int'l L.*, 50, p. 719.

Borges, A. *Reimagining the 'E' in O.E.E. in the Packaging Industry | Packaging Strategies*. *Packaging Strategies*. Available at: https://www.packagingstrategies.com/articles/95809-reimagining-the-e-in-oee-in-the-packaging-industry (Accessed: 15 April 2023).

Buckley, G.J. *et al.* (2013) *The Effects of Falsified and Substandard Drugs*. National Academies Press (U.S.) Available at: https://www.ncbi.nlm.nih.gov/books/NBK202526/ (Accessed: 8 April 2023).

Butschli, J. (2017) 'Serialization Implementation Improves Par Pharma's Efficiency'. *Packaging World*, 3 August. Available at: https://www.packworld.com/issues/operational-excellence/article/13373125/serialization-implementation-improves-par-pharmas-efficiency (Accessed: 25 May 2020).

Casali, N. (2019) *College of Engineering and Management Master of Science in Engineering and Management Master of Science Thesis Increasing the O.E.E. of an Oral Solutions Production Line by Applying Lean Manufacturing Tools Supervisor: Candidate: Domenico Augusto Maisano Casali Nicolas April 2019*. [Master's Thesis Thesis]. Torino: POLITECNICO DI TORINO. Available at: https://webthesis.biblio.polito.it/10613/1/tesi.pdf (Accessed: 18 June 2020).

Center for Drug Evaluation and Research. (2018) Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers (Accessed: 18 July 2020).

Chatterjee, B. (2014) *Applying Lean Six Sigma in the Pharmaceutical Industry*. 1st Edition. Routledge Available at: https://doi.org/10.4324/9781315567419.

Cockburn R, Newton PN, Agyarko EK, Akunyili D, White NJ (2007) Correction: The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the Dangers. PLOS Medicine 4(9): e289. https://doi.org/10.1371/journal.pmed.0040289

COMMISSION OF THE EUROPEAN COMMUNITIES. (2008a) *COMMISSION STAFF WORKING DOCUMENT Accompanying Document to the Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL Amending Directive 2001/83/E.C. as Regards the Prevention of the Entry into the Legal Supply Chain of Medicinal Products Which Are Falsified in Relation to Their Identity, History or Source Impact*. COMMISSION OF THE EUROPEAN COMMUNITIES Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52008SC2674&from=en (Accessed: 18 June 2020).

COMMISSION OF THE EUROPEAN COMMUNITIES. (2008b) Available at: https://ec.europa.eu/health/sites/health/files/files/pharmacos/pharmpack_12_2008/counterfeit-ia_en.pdf.

Cordon, C. *et al.* (2016) 'Serialization in the Pharmaceutical Industry'. *Strategy Is Digital: How Companies Can Use Big Data in the Value Chain*, pp. 47–64.

Deloitte. (2012) *Vaccine 2D Barcoding for Manufacturers - IIS | CDC*. *www.CDC.gov*. Available at: https://www.cdc.gov/vaccines/programs/iis/2d-barcodes/manufacturers.html (Accessed: 8 April 2023).

Discover CI. (2020) *TEVA | Inventory Turnover Chart and History 2017-2020 | DiscoverCI*. Available at: https://www.discoverci.com/companies/TEVA/inventory-turnover (Accessed: 2 August 2020).

EFPIA. (2012) *EFPIA Individual Response. Coding & Serialisation Delegated Act on the Detailed Rules for a Unique Identifier for Medicinal Products for Human Use, and Its Verification Concept Paper Submitted for Public Consultation EFPIA Individual Response*. EFPIA Available at: https://ec.europa.eu/health/sites/health/files/files/falsified_medicines/2012-06_safety-features/efpia_en.pdf (Accessed: 14 July 2020).

EUIPO. and OECD. (2020) *Trade in Counterfeit Pharmaceutical Products*. Available at: https://euipo.europa.eu/tunnel-web/secure/webdav/guest/document_library/observatory/documents/reports/Trade_in_Counterfeit_Pharmaceutical_Products/Trade_in_Counterfeit_Pharmaceutical_Products_en.pdf (Accessed: 17 June 2020).

EUIPO. and OECD. (2019) *Trends in Trade in Counterfeit and Pirated Goods*. OECD Publishing, Paris/European Union Intellectual Property Office Available at: https://euipo.europa.eu/tunnel-web/secure/webdav/guest/document_library/observatory/documents/reports/trends_in_trade_in_counterfeit_and_pirated_goods/trends_in_trade_in_counterfeit_and_pirated_goods_en.pdf (Accessed: 5 July 2020).

European Commission. (2008) *2007 REPORT ON COMMUNITY CUSTOMS ACTIVITIES ON COUNTERFEIT AND PIRACY RESULTS AT THE EUROPEAN BORDER - 2007 2 European Commission —*

Taxation and Customs Union. Available at: https://ec.europa.eu/taxation_customs/sites/taxation/files/resources/documents/customs/customs_controls/counterfeit_piracy/statistics2007.pdf (Accessed: 22 June 2020).

European Commission. (2012) *2011 REPORT ON COMMUNITY CUSTOMS ACTIVITIES ON COUNTERFEIT AND PIRACY RESULTS AT THE EUROPEAN BORDER*. Available at: https://ec.europa.eu/taxation_customs/sites/taxation/files/resources/documents/customs/customs_controls/counterfeit_piracy/statistics/2012_ipr_statistics_en.pdf (Accessed: 22 June 2020).

European Commission. (2019) *2018 REPORT ON COMMUNITY CUSTOMS ACTIVITIES ON COUNTERFEIT AND PIRACY RESULTS AT THE EUROPEAN BORDER - 2018 2 European Commission — Taxation and Customs Union*. Available at: https://ec.europa.eu/taxation_customs/sites/taxation/files/2019-ipr-report.pdf (Accessed: 22 June 2020).

European Commission. (2017) *EudraLex - Volume 4 - Good Manufacturing Practice (G.M.P.) Guidelines - Public Health - European Commission*. *Public Health*. Available at: https://ec.europa.eu/health/documents/eudralex/vol-4_en (Accessed: 16 December 2018).

EUROPEAN COMMISSION Enterprise + Industry. (2008) *Counterfeit Medicines - Responses to Public Consultation (2008)*. Available at: https://web.archive.org/web/20090109020934/http://ec.europa.eu/enterprise/pharmaceuticals/counterf_par_trade/counterfeit_consult_2008.htm#i (Accessed: 14 July 2020).

European Medicines Agency. (2018) *European Medicines Agency Recommends Measures to Manage Contamination of Heparin-Containing Medicines*. *European Medicines Agency*. Available at: https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-measures-manage-contamination-heparin-containing-medicines (Accessed: 3 July 2020).

European Medicines Verification System. (2023) *EMVO*. Available at: https://emvo-medicines.eu/ (Accessed: 8 April 2023).

Europol. (2020) *€7.9 MILLION OF ILLEGAL PRODUCTS SEIZED IN A HIT AGAINST MEDICINE TRAFFICKERS*. Available at: https://www.europol.europa.eu/print/newsroom/news/%E2%82%AC79-million-of-illegal-products-seized-in-hit-against-medicine-traffickers (Accessed: 29 June 2020).

Fortier, S. and Joevan, A. (2017) 'How Serialization Can Improve Drug Manufacturing Operations'. *Manufacturing Engineering;*

Friedli, T. *et al.* (eds.) (2013) *Leading Pharmaceutical Operational Excellence: Outstanding Practices and Cases*. Berlin Heidelberg: Springer-Verlag DOI: 10.1007/978-3-642-35161-7.

Griffith, C.M., Rondoletto, N. and Hamed, F. (2010) 'Genentech Journey to Operational Excellence 2004 - 2009'. In *The Pathway to Operational Excellence in the Pharmaceutical Industry – Overcoming the Internal Inertia*. University of St. Gallen, pp. 135–137. Available at: https://www.swisscleanroomconcept.ch/UserFiles/File/ECV%20Leseproben/the-pathway-to-operational-excellence.pdf.

GS1 AISBL. (2013) Available at: https://www.gs1ie.org/download_files/healthcare_files/gs1-datamatrix-in-healthcare.pdf (Accessed: 12 July 2020).

GS1 Ireland. (2023) *Pharma Serialisation and the E.U. Falsified Medicines Directive*. Available at: https://www.gs1ie.org/healthcare/sectors/pharma/pharma-serialisation-and-the-eu-falsified-medicines-directive.html (Accessed: 15 April 2023).

Gyurjyan, G. *et al.* (2017) *Rethinking Pharma Productivity | McKinsey*. Available at: https://www.mckinsey.com/industries/life-sciences/our-insights/rethinking-pharma-productivity (Accessed: 15 April 2023).

Hall, C. (2012) 'Technology for Combating Counterfeit Medicine'. *Pathogens and Global Health*, 106(2), pp. 73–76.

Harris, G. and Bogdanich, W. (2008) 'Drug Tied to China Had Contaminant, F.D.A. Says'. *The New York Times*, 6 March. Available at: https://www.nytimes.com/2008/03/06/health/06heparin.html (Accessed: 3 July 2020).

Hayes, R.H. and Wheelwright, S.C. (1984) 'Restoring Our Competitive Edge: Competing Through Manufacturing'. Available at: https://www.hbs.edu/faculty/Pages/item.aspx?num=47196 (Accessed: 25 July 2020).

Hubbard, W.K. (2009) 'Can the Food and Drug Administration Ensure That Our Pharmaceuticals Are Safely Manufactured?' *Archives of Internal Medicine*, 169(18), pp. 1655–1656. DOI: 10.1001/archinternmed.2009.304.

International Federation of Pharmaceutical Manufacturers and Associations. (2023) *Falsified Medicines*. *IFPMA*. Available at: https://ifpma.org/areas-of-work/improving-health-security/falsified-medicines/ (Accessed: 8 April 2023).

IRACM. and Przyswa, eric. (2013) *Counterfeit Medicines and Criminal Organizations*. International Institute of Research Against Conterfeit Medicines Available at: http://fightthefakes.org/wp-content/uploads/2013/11/Rapport-Etude_IRACM_Contrefacon-de-Medicaments-et-Organisations-Criminelles_EN_FINALs2.pdf (Accessed: 30 June 2020).

ISO. (2006) Available at: https://www.sis.se/api/document/preview/907850/ (Accessed: 14 July 2020).

Jablonski, J. and Brochu, D. (2006) 'Manufacturing Business Intelligence Technology Drives Operational Excellence'.

LAHJOUJI, M. *et al.* (2023) 'A SYSTEMATIC LITERATURE REVIEW: THE POWER OF THE BLOCKCHAIN TECHNOLOGY TO IMPROVE PHARMACEUTICAL SUPPLY CHAIN'. *Journal of Theoretical and Applied Information Technology*, 101(2).

Liang, B. (2006) 'Parallel Trade in Pharmaceuticals: Injecting the Counterfeit Element into the Public Health'. *North Carolina Journal of International Law*, 31(4), p. 847.

Mackey, T.K. *et al.* (2015) (5) 'After Counterfeit Avastin ® —What Have We Learned and What Can Be Done?' *Nature Reviews Clinical Oncology*, 12(5), pp. 302–308. DOI: 10.1038/nrclinonc.2015.35.

Mahood, Q., Van Eerd, D. and Irvin, E. (2014) 'Searching for Grey Literature for Systematic Reviews: Challenges and Benefits'. *Research Synthesis Methods*, 5(3), pp. 221–234. DOI: 10.1002/jrsm.1106.

Mankins, M. (2017) 'Great Companies Obsess Over Productivity, Not Efficiency'. *Harvard Business Review*, 1 March. Available at: https://hbr.org/2017/03/great-companies-obsess-over-productivity-not-efficiency (Accessed: 30 July 2020).

MOSSINGHOFF, G.J. (1999) 'Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process'. *FOOD AND DRUG LAW JOURNAL*, 54, p. 8.

Nakajima, S. (1988) *Introduction to TPM: Total Productive Maintenance. (Translation)*.

Nalam, R. (2023) 'Systematic Review of Pharmaceutical Drugs Serialization'. *Systematic Review of Pharmaceutical Drugs Serialization*, 120(1), pp. 9–9.

Nguyen, A. *et al.* (2023) 'On the Use of Logistics Data to Anticipate Drugs Shortages through Data Mining'. *Procedia Computer Science*, 219, pp. 949–956.

OECD/EUIPO. (2020) *Trade in Counterfeit Pharmaceutical Products, Illicit Trade*. OECD Publishing, Paris: OECD/EUIPO Available at: https://doi.org/10.1787/a7c7e054-en.

O'Mahony, D. (2020) *The Impact of Serialisation on Operational Efficiency and Productivity in Irish Pharmaceutical Sites*. Dublin: Griffith College. Available at: https://go.griffith.ie/427/1/77792_Daniel_OMahony_Dan_O_Mahony_Dissertation_Submission_2976250_216874_802618486%20(1).pdf.

Ozkaya, E., Wizard, S.C., and L.L.C. (2017) *Digital Factory Transformation beyond Serialization Compliance*. *Pharmaceutical Commerce*. Available at: https://pharmaceuticalcommerce.com/manufacturing-and-packaging/digital-factory-transformation-beyond-serialization-compliance/ (Accessed: 17 July 2020).

Pappas, C. and Williams, I. (2011) 'Grey Literature: Its Emerging Importance'. *Journal of Hospital Librarianship*, 11(3), pp. 228–234.

Penfold, Alfred.W. (2018) *How to Minimize Impact on Overall Equipment Effectiveness (O.E.E.)*. *ISPE | International Society for Pharmaceutical Engineering*. Available at: https://ispe.org/pharmaceutical-engineering/ispeak/how-to-minimize-impact-overall-equipment-effectiveness-oee (Accessed: 8 April 2023).

Penfold, A.W. (2018) *ISPE: How to Minimize Impact on Overall Equipment Effectiveness (O.E.E.)*. *ISPE | International Society for Pharmaceutical Engineering*. Available at: https://ispe.org/pharmaceutical-engineering/ispeak/how-to-minimize-impact-overall-equipment-effectiveness-oee (Accessed: 6 January 2020).

Pew Charitable Trusts. and Booz Allen Hamilton. (2013) *Implementing a Pharmaceutical Serialization and Traceability System in the United States*.

Pew Foundation. and Booz Allen Hamilton. (2014) *P.E.W. Booz Allen Hamilton Report Evaluating The Economic Impact Of Item Serialization*. Available at: https://www.pewtrusts.org/-/media/assets/2014/04/29/boozallenhamiltonreport.pdf (Accessed: 19 July 2020).

Pharma Logistics I.Q. (2017) *Pharmaceutical Serialization and Traceability: 2017 Trend Report*. *Pharma Logistics*. Available at: https://www.pharmalogisticsiq.com/supply-chain-security-track-trace/whitepapers/pharmaceutical-serialization-and-traceability-2017 (Accessed: 8 April 2023).

Pharma Manufacturing. (2007) 'Benchmarking Shows Need to Improve Uptime, Capacity Utilization'. *Pharma Manufacturing*. Available at: https://www.pharmamanufacturing.com/articles/2007/144/ (Accessed: 21 June 2020).

Pharmaceutical Security Insitute. (2023) *Incident Trends*. *P.S.I*. Available at: https://www.psi-inc.org/incident-trends (Accessed: 8 April 2023).

Pirrera, V. and Jordan, J. (2014) *Reclaiming Efficiency Amid Serialization Nightmares*. Available at: https://www.vantage-cg.com/wp-content/uploads/2018/07/serialization-nightmares.pdf.

Pisani, E. (2017) (978-92-4-151342–5) *WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products*. World Health Organization Available at: https://apps.who.int/iris/bitstream/handle/10665/326708/9789241513425-eng.pdf?ua=1 (Accessed: 20 June 2020).

Rajora, N. (2023) (2) 'Essence Controls in Pharmaceutical Enterprise Systems'. *International Journal of Science and Research Archive*, 8(2), pp. 012–017. DOI: 10.30574/ijsra.2023.8.2.0197.

Ramesh, A. (2015) '"Bridging the Value Chain"–The Pedigree Way'.

Rethinking Pharma Productivity | McKinsey. Available at: https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/rethinking-pharma-productivity (Accessed: 17 May 2021).

Robinson, P. *et al.* (2013) *Evaluation of the Impact of 2D Barcodes on Vaccine Secondary Packaging*. Center for Immunization and Respiratory Diseases Immunization Services Division Centers for Disease Control and Prevention: C.D.C. Available at: https://www.cdc.gov/vaccines/programs/iis/2d-vaccine-barcodes/downloads/secondary-packaging-evaluation.pdf (Accessed: 19 July 2020).

Rodgers, D. (2014) *Impact on Production Line Speeds and O.E.E*. Healthcare Packaging Available at: https://www.healthcarepackaging.com/issues/traceability-serialization/article/13288019/impact-on-production-line-speeds-and-oee (Accessed: 17 July 2020).

Rodgers, D. (2015) *Serialization Playbook*. *Healthcare Packaging*. Available at: https://www.healthcarepackaging.com/logistics-distribution/logistics-supply-chain/document/13686132/serialization-playbook (Accessed: 8 April 2023).

de Ron, A.J. and Rooda, J.E. (2006) 'O.E.E. and Equipment Effectiveness: An Evaluation'. *International Journal of Production Research*, 44(23), pp. 9–15. DOI: 10.1080/00207540600573402.

Rotunno, R. *et al.* (2014a) 'Impact of Track and Trace Integration on Pharmaceutical Production Systems'. *International Journal of Engineering Business Management*, 6, p. 25. DOI: 10.5772/58934.

Rotunno, R. *et al.* (2014b) 'Impact of Track and Trace Integration on Pharmaceutical Production Systems': *International Journal of Engineering Business Management*, p. 9. DOI: 10.5772/58934.

Sarkar, S. (2022) 'Pharmaceutical Serialization: A Challenge for Small Manufacturers'. *International Journal of Scientific Research in Computer Science, Engineering and Information Technology*, 8(4), pp. 174–181.

Schonberger, R.J. (2007) *Best Practices in Lean Six Sigma Process Improvement: A Deeper Look | Wiley*. Wiley Available at: https://www.wiley.com/en-us/Best+Practices+in+Lean+Six+Sigma+Process+Improvement%3A+A+Deeper+Look-p-9780470168868 (Accessed: 25 July 2020).

Shanley, A. (2016), "Serialization: Getting Past the Quick Fix", *BioPharm*, Vol. 40 No. 1, pp. 65–68.

Trajanovska, I., Pavicevic, B., Brezovska, K., Jolevska, S.T. and Ribarska, J.T. (2023), "Principles and methods used in the serialization process of the medicines", *Macedonian*

Pharmaceutical Bulletin, Vol. 68 No. 1, pp. 203–204, doi: 10.33320/maced.pharm.bull.2022.68.03.097.

Singh, R.K., Kumar, R. and Kumar, P. (2016) 'Strategic Issues in Pharmaceutical Supply Chains: A Review'. *International Journal of Pharmaceutical and Healthcare Marketing*, 10(3), pp. 234–257.

Spector, R. (2018) *Lean Laggards: Exploring the State of Lean in Pharma*. *Pharma Manufacturing*. Available at: https://www.pharmamanufacturing.com/articles/2018/lean-laggards-exploring-the-state-of-lean-in-pharma/ (Accessed: 27 July 2020).

Starke, V. and Kumor, J. (2013) 'Abbott Pharmaceuticals Journey of Business Excellence Standards'. In Friedli, T. et al. (eds.) *Leading Pharmaceutical Operational Excellence: Outstanding Practices and Cases*. Berlin, Heidelberg: Springer, pp. 153–168. DOI: 10.1007/978-3-642-35161-7_11.

Trajanovska, I., Pavicevic, B., Brezovska, K., Jolevska, S.T. and Ribarska, J.T. (2023), "Principles and methods used in the serialization process of the medicines", Macedonian Pharmaceutical Bulletin, Vol. 68 No. 1, pp. 203–204, doi: 10.33320/maced.pharm.bull.2022.68.03.097.

Vander Beken, T. and Balcaen, A. (2006) 'Crime Opportunities Provided by Legislation in Market Sectors: Mobile Phones, Waste Disposal, Banking, Pharmaceuticals'. *European Journal on Criminal Policy and Research*, 12(3), pp. 299–323. DOI: 10.1007/s10610-006-9025-0.

Vernon, J.A., Hughen, W.K. and Trujillo, A.J. (2007) 'Pharmaceutical Manufacturing Efficiency, Drug Prices, and Public Health: Examining the Causal Links'. *Drug Information Journal*, 41(2), pp. 229–239. DOI: 10.1177/009286150704100217.

Werani, J., Bellando Randone, G. and Goetzfried, M. (2010) 'Making Operational Excellence Work – Training and Coaching Supporting Behavioral Change'. In *The Pathway to Operational Excellence in the Pharmaceutical Industry – Overcoming the Internal Inertia*. University of St. Gallen, p. 10. Available at: https://www.swisscleanroomconcept.ch/UserFiles/File/ECV%20Leseproben/the-pathway-to-operational-excellence.pdf.

WHO. (2013) *WHO | Deadly Medicines Contamination in Pakistan*. *WHO*. Available at: https://www.who.int/features/2013/pakistan_medicine_safety/en/ (Accessed: 4 July 2020).

WHO. (2003) Available at: https://web.archive.org/web/20041125080255/http://www.who.int/mediacentre/factsheets/fs275/en/print.html.

Willis, M. (2017) 'Data Management: Standards, Security, Integrity and Analytics'.[PDF] Available at: https://www.researchgate.net/publication/322084122_Pharmaceutical_Serialisation_Data_Management.

World Health Organisation. (2023) *Substandard and Falsified Medical Products*. *WHO.int*. Available at: https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products (Accessed: 8 April 2023).