The impact of serialisation on operational efficiency and productivity in Irish pharmaceutical sites

By

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A thesis submitted in partial fulfilment of the requirements for MSc in Pharmaceutical Business & Technology (QQI)

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August 2020

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Signed  **Date: 19th August 2020**

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2. Acknowledgements

I would like to thank my wife Michelle for her support, guidance and inspiration while writing this thesis. My parents in law, Anne and Christy have been a constant support helping with the work that I did not get to do, while studying.

Alan Lynch, my supervisor deserves great credit for remaining calm as deadlines loomed.

Finbarr Sheehy and all the staff in Innopharma Labs and Griffith College must be thanked for creating a great learning experience. Without wishing to overstep the mark I would like to thank the creators of Springboard courses who have provided educational opportunities for many.

Frank Madden and all the team in Crest Solutions Ltd, who provided me with the opportunity to work in the pharmaceutical services industry and gave me the basis for this thesis and a network of companies that I could approach to discuss the topic.

I would like to thank Padraig Henry and Neal Johnson from my former employer, Exertis Supply Chain Solutions, who supported me as I started out in the industry.

I would like to thank all those companies that gave up their valuable time to participate in the interview and survey.

3. List of Figures and Tables

4. List of Acronyms

3PL	Third Party Logistics
AFSSAPS	Agence Francasie de Securite Sanitaire des Produits de Sante
API	Active Pharmaceutical Ingredients
ASOP	Alliance for Safe Online Pharmacy
BAU	Business as usual
BEUC	Bureau Européen des Unions de Consommateurs
CDC	Center for Disease Control
CDER	Center for Drug Evaluation and Research
CMO	Contract Manufacturing Organization
CMPI	Centre for Medicines in the Public Interest
COGS	Cost of Goods Sold
CPO	Contract packing Organization
DMC	Data Matrix code
DSCSA	Drug Supply Chain Security Act
E.C.	European Commission
EAHP	European Association of Hospital Pharmacists
EDI	Electronic Data Interchange
EFPIA	European Ferderation Pharmaceutical Industry Associations
EMA	European Medicines Agency
EMS	Effective management Systems
EMVO	European Medicines Verification Organization
EU	Europea Union
EUIPO	European Union Intellectual Property Organisation
FDA	U.S. Food and Drug Adminstration
FDAAA	Food and Drug Administration Ammendments Act
FMD	Falsified Medicines Directive
GDSN	Global Data Sharing Metwork
GMP	Good Manufacturing Practice
GS1	Glogal Standards One
GSK	Glaxo Smithkline
GTIN	Global Tracking Identification Number
HBR	Harvard Business Review
HPRA	Healthcare Products Regulatory Authority
HUG	Healthcare User Group
IBEC	Irish Employers and Business Confederation
ICDRA	International Conferences of Drug Regulatory Authorities
IDA	Industrial Development Authority
IFPMA	International federation of Pharmaceutical Manufacturing Associastions
IMPACT	International Medicinal Products Anti Counterfeiting Taskforce
IPC	In Process Control

ISO	International Standards Organisation
ISPE	International Society for Pharmaceutical Engineering
JIT	Just in Time
KPI	Key performance indicator
MAH	Marketing Authorisation Holder
MSD	Merck Sharpe Dohme
NDC	National Drug Code
NMVO	National Medicines Verification organisation
OECD	Organization for Economic Cooperation and Development
OEE	Overall Equipment Effectiveness
OEEML	Overall Equipment Effectiveness of a Manufacturing Line
OEM	Original Equipment Manufacturer
OPEX	Operational Excellence
PDMA	Prescription Drugs Marketing act
PhRMA	Pharamceutical Research based Manufacturing Association
PPM	Parts per minute
PSI	Pharmaceutical Security Institute
RAM	reliability Avaialability Maintenance
RFID	Radio Frequency Identification
SEMI	Semiconductor Equipment and Materials International
SME	Subject Matter Expert
SNI	Standardized Numerical Identification
SOP	Standard Operating Procedure
TPM	Total Productive Maintenance
TQM	Total Quality Maintenance
UHF	Ultra High Frequency
WHA	World Healthcare Assembly
WHO	World healthcare Organization

5. Abstract

Serialisation technology was introduced to protect the pharmaceutical supply chain from infiltration by falsified and substandard medicines. The implementation of serialisation systems required a substantial investment by pharmaceutical manufacturers. This study investigated the impact of serialisation on the operational efficiency and productivity in Irish pharmaceutical sites. Ireland plays an important role in the global pharmaceutical manufacturing network. All of the top ten largest pharmaceutical companies have manufacturing operations in Ireland. A review of the literature showed only limited publications on the topic of serialisation, operational efficiency, and productivity, particularly in the Irish context. A research method was designed to assess the relationship between serialisation, operational efficiency, and productivity. The research consisted of a survey and interview process with 11 manufacturing sites in Ireland. Participating companies operated a total of 114 pack-lines, representing approximately 65% of the automated packing lines in the country. The research focused on measurements such operational equipment effectiveness (OEE), line availability, unit cost and cost per pack. The study revealed that serialisation had a negative impact on pack line OEE and line availability. The research found that serialisation had a negative impact on the unit cost of packaged pharmaceuticals. The study assessed the expected costs of serialisation with the actual costs experienced by manufacturers. The research found that the actual capital costs of serialisation were four times greater than the costs originally outlined by policymakers. The study identified a trend where Irish pharmaceutical sites are moving away smaller batch production and moving toward larger batches so as to gain greater efficiencies, The research also proposed the use of a serialisation depreciation factor (SD_f) as a method to determine the impact of serialisation on the cost of goods sold.

Keywords:

Pharmaceutical Cost of Goods Sold, Pharmaceutical COGS, Pharmaceutical OEE, Serialisation OEE

6. Introduction

Since the 1980s the World Health Organization (WHO) 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. 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. Regulatory authorities started to take action to protect patients. Governments realised the strategic importance of the pharmaceutical industry and the scale of the threat posed by illegal medicines. Governments and regulators worked together to implement legislation designed to protect the legitimate pharmaceutical sales channels. The pharmaceutical industry also realised the danger posed by criminals operating in their industry. The risk to patient safety, reputational damage and the loss of revenue focused the pharmaceutical industry's attention on counterfeit medicines.

The introduction of anti-counterfeiting regulations has required a large investment by the pharmaceutical industry in new equipment and resources. The regulations introduced to protect pharmaceutical supply chains use serialisation technology to print a unique identifier on each pack of medicine. Every carton, bottle or vial of medicine produced for the U.S. and European markets must carry a serialised code that is unique to that pack. The serial code, expiry date and batch number are contained in a 2D matrix code mandated in regulations. See Figure 1. Serial codes are decommissioned at the point of dispensing by a pharmacist.

Figure 1 An example of a 2D Matrix Code (GS1 Ireland and Enterprise System Partners, 2016)

To print and check a 2D Matrix code is simple. To flawlessly print 200 codes per minute on a 24/7 cycle shift requires a great deal of skill and resources. Unit level serialisation creates a large amount of data that must be stored, retrieved, and communicated across multiple systems. A large pharmaceutical company will produce 650 GB of serialisation 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.

The purpose of this research is to assess the impact of serialisation on the efficiency and productivity of Irish pharmaceutical sites. The first objective of this research was to determine if the assumptions and predictions outlined in the literature regarding the impact of serialisation on production efficiency were correct. With the benefit of hindsight and given the data now available the research sought to find if policy makers and industry representatives fully appreciated the impacts of serialisation at the factory floor level.

The next objective was to quantify the impact of serialisation on operational efficiency using measurements such as Operational Equipment Effectiveness (OEE) and production line availability measures. Serialisation inherently requires the addition of new process steps into existing operations. The addition of new processes might infer a reduction in OEE. Conversely the addition of new equipment might increase OEE levels. The research looked at the literature to gain insight into the experiences of manufacturers in the post serialisation era. A research methodology was designed to assess Irish manufacturers experience with serialisation and OEE.

The last objective was to determine if serialisation processes had an impact on site productivity. Serialisation required a substantial investment by the pharmaceutical industry in terms of capital expenditure. New expertise and resources were required to manage and operate serialisation system and to store and distribute data. Did this expenditure impact the cost of goods sold (COGS)? Did serialisation track and trace systems bring greater productivity by providing manufacturers with better data to manage supply chains? Productivity changes were measured using changes to the cost of goods sold (COGS) and unit pricing. The research also examined if the phenomena of serialisation and the trend toward operational excellence techniques coincided with each other to create a greater impact on productivity. If a trend toward smaller batch sizes coincided with the implementation of serialisation processes could these two changes in production process have exacerbated each other?

To determine what information was currently available to inform the research objectives a literature review was conducted. The purpose of the literature review was to:

(i) identify what consideration was given by policy makers and industry bodies as to the impact of serialisation on operational efficiency in the pre-serialisation phase and in the period after the implementation of serialisation processes

(ii) Identify from the literature what information was available on the impact of serialisation on operational efficiency and to identify gaps in the literature that could be used to create a research model that could add to knowledge of the subject

(iii) Identify from the literature what information was available on the impact of serialisation on pharmaceutical site productivity. To identify gaps in the literature that could be used to create a research model that could add to knowledge of the subject

Following a review of the literature a research methodology was designed that sought data and input from Irish pharmaceutical manufacturing sites. The survey and interview process was broken into three sections. The first section was designed to understand the participants background and to determine the serialisation resources available at the company. This section sought to contrast the site's actual serialisation experience with assertions found in the literature review.

The second section of the semi structured interview process examined the impact of serialisation on operational efficiency by discussing OEE measurements and line availability measurements. Participants were shown part of a 2018 article published in the ISPE magazine where the impact of serialisation on OEE was discussed. Participants were asked to share their experiences of serialisation and OEE measurements. Respondents were also asked to comment on pack line availability.

The final part of the assessment dealt with the serialisation and productivity. Participants were asked about the impact of serialisation on the Cost of Goods Sold (COGS). The final

section of the survey and interview also examined the relationship between average batch size, serialisation, and productivity.

Data from the research was collated and the experience of different manufacturing sites was examined to create a series of findings. The findings drew upon the research survey data as well as input from interviews conducted with subject matter experts. The findings from the research was examined to draw up a series of conclusions and also to identify areas of further research.

7. Literature Review

The literature review supported the main aim of the research to determine the impact of serialisation on operational efficiency and productivity on Irish 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. Gaps identified in the literature were used to inform the methodology for the research. The literature review was conducted in three phases. The first phase of the literature review examined on how and why policies were developed to tackle counterfeit medicines. This section also examined the scale of the falsified medicines issue and how serialisation technology was chosen as the tool to protect the legitimate pharmaceutical supply chain. This section of the literature review also examined how policy makers and industry stakeholders considered the impact of serialisation processes on operational efficiency and productivity. Did policy makers and industry bodies consider efficiency and productivity during the formulation of serialisation regulations and its impact in the post serialisation period?

The next phase of the literature review examined the available literature on how operational efficiency is measured in the pharmaceutical industry. A search was conducted to find articles on how the pharmaceutical industry adopted serialisation technology and if serialisation 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 on the cost of goods sold and unit cost were examined. The literature review sought to examine articles on the relationship between serialisation and unit cost.

Literature Review Strategy		
Phase	**Topic**	**Sources**
Phase I	Development of serialisation policies and the considerations given to efficiency and productivity in policy development	E.C. Reports, Interpol, EUIPO Reports, ASOP, WHO, FDA, U.S. Congress
Phase II	Measurement of operational efficiency in the pharmaceutical industry and the impact of serialisation	E.C. Reports, FDA Reports, Industry journal articles and industry magazines,
Phase III	Measurement of productivity in the pharmaceutical industry and the impact of serialisation on productivity in pharmaceutical packaging companies	E.C. Reports, FDA Reports, Industry journal articles and industry magazines,

Table 1 Literature review strategy

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 which included both the UK spelling of "serialisation" and the U.S. spelling "serialization". Variations of "operational effiectiveness", "OEE", "Operational Excellence", "OPEX" and "impact" were used in the Boolean searches.

7.1 Ireland's role in combatting counterfeit medicines

Ireland plays an important role in the fight against counterfeit medicines. Irish based pharmaceutical companies must meet the regulatory demands of all the markets supplied from Ireland. Leading pharmaceutical companies such as Johnson & Johnson, MSD, Amgen, Pfizer, Gilead, Abbvie and Sanofi have manufacturing operations in Ireland. (IDA, 2020). All ten of the global top ten pharmaceutical companies have manufacturing operations in Ireland. The value of pharmaceutical exports from Ireland in 2018 was €73bn. (IBEC, 2019). Irish based pharmaceutical companies produce active pharmaceutical ingredients (API) and bulk biologic medicines as the raw material for other global pharmaceutical sites. Semi-finished vials and fully packaged medicines are also supplied for global markets. The Irish regulator, HPRA (Health Products Regulatory Authority) oversees pharmaceutical manufacturing activities in Ireland. Irish based manufacturers must meet the good manufacturing practise (GMP) and quality management standards of all the markets served including the U.S. Food and drug Administration (FDA). The majority of Ireland's 2019 exports

(€39bn) going to the U.S. market are made up of pharmaceutical products. (Gov.ie, 2019). While Irish based pharmaceutical companies will meet the regulatory demands of all the markets they supply, the EMA and FDA take a leading role in regulatory development and expectation.

7.2 Scale of the trade in counterfeit medicines

Estimations vary on the value of trade in counterfeit medicines. There is consensus that sub-standard and falsified medicines present an enormous risk to patient safety and to the legitimate medicines supply chain. One analysis by the Havoscope company, who specialise in black market research put the direct value of the counterfeit drugs trade at $200bn per annum (Havoscope, 2020).

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. 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).

The difficulty in compiling comprehensive data is particularly acute in developing countries. In an interview, Dr. Paul Newton Head of the Wellcome Trust Tropical medicines research program in Laos said that "the paucity of reliable data means that it is difficult to know whether the problem is getting better or worse, how the epidemiology of substandard and falsified medicines differ and whether interventions are effective" (Newton *et al.*, 2001).

7.3 Pharmaceutical supply chains complexity

Pharmaceutical supply chains are complex and stretch across the globe. Pharmaceutical brands may decide to manufacture products at their own facilities, or they may decide to use a contract manufacturing organization (CMO). Raw materials may come from low cost economies such as China or India. Pharmaceutical brands may use contract partners to manufacture raw materials on their behalf. A pharmaceutical company may fill semi-finished product into primary packaging at their own facilities but may then have an outsourced contract packaging organization (CPO) 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 to a licensed wholesaler/distributor.

The complexity of the pharmaceutical supply chain is highlighted in Figure 1, sourced from a WHO report on counterfeit medicines. (Pisani, 2017)

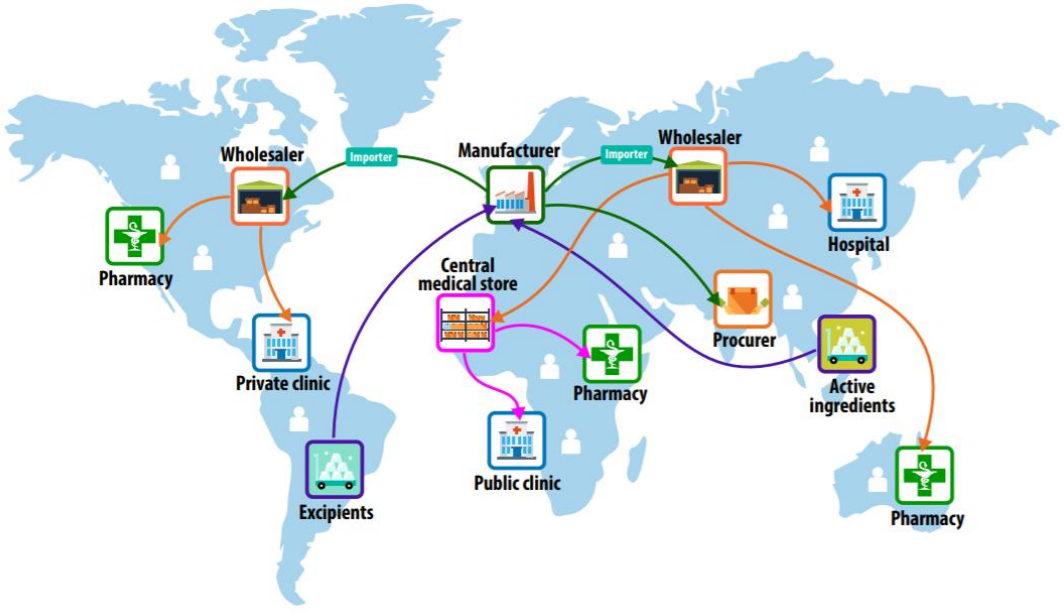


Figure 2 Pharmaceutical Supply Chain Complexity. Source WHO Global Surveillance and Monitoring System for substandard and falsified medical products (Pisani, 2017)

The complexity of the pharmaceutical supply chain makes it susceptible to infiltration both in terms of sub-standard raw materials and fake finished products. The adoption of serialisation systems is just one of the tools used to combat illegal medicine supply.

7.4 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 the 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 the fake Heparin caused the death of 81 patients in the U.S. (Harris and Bogdanich, 2008). The contaminated Heparin caused a Serratia Marcescens bacterial infection. In one outpatient treatment clinic in Texas the use of the fake Heparin caused infections in 67 patients, many of whom were recovering cancer patients. (Su *et al.*, 2009). There were also reports of infections from the counterfeit Heparin in the EU, though thankfully 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 the

treatment of tumours. Avastin achieved sales of $6bn USD in 2012. The product cost about $2,500 per dose. The counterfeit medicine entered the U.S. market via an online website Canadadrugs.com. When U.S. regulators tested the fake Avastin they found it contained no active pharmaceutical ingredients. (Mackey *et al.*, 2015)

The Canadian distributor relabelled a Turkish market version of Avastin, branded Altuzan, from a UK wholesaler. The British wholesaler had purchased the counterfeit medicine from a Danish company who in turn had purchased the product from a Swiss dealer who sourced it from an Egyptian distributor via a Syrian dealer. The Avastin scandal is an excellent example of the complexity of the global pharmaceutical supply chain and the difficulties involved in protecting legitimate sales channels from unscrupulous agents. (IRACM and Przyswa, 2013)

In another 2002 case, criminals in Florida relabelled 110,000 doses of the drug Epogen (AGOVINO, 2002). Epogen is used as a treatment for anaemia and is used as a drug therapy in chemotherapy and late stage kidney failure. Patients reported, painful adverse reactions to the fake Epogen. By relabelling vials with a lower concentration of the drug as having a higher strength the criminals netted a $46m USD profit. (PEW Health Group, 2013) Only 10% of the counterfeit drugs put into circulation by the criminal gang were ever recovered. (Thompson, 2003)

Data from the seizure of illicit medicines data can provide some insight into the scale of the counterfeit medicines threat. Each year a report is compiled detailing customs activities across all the EU member states. Only a small percentage of counterfeit drugs coming from outside the customs union ever get caught by customs officials. However, the customs union wide report presents an overall picture of the situation for falsified medicines and can help determine some of the scale of the challenge. 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). We can see that at the time of policy formation regrading falsified medicines and serialisation that the threat of unlicensed drugs was growing at an alarming rate. Even allowing for growth in EU membership and more effective action from customs officers the trend was certainly going in the wrong direction. By 2013, prior to the introduction of serialisation controls, the situation had started to reverse. 2013 numbers were half that of 2011 with 3.6m articles seized to a retail value of €11.9m (European Commission,

2014). By 2017, the situation showed even greater improvements with only 0.5m items seized with a retail value of €6.9m (European Commission, 2017a). Numbers from the latest 2018 report are even lower again with 166,000 articles seized with a retail value of just over €4m (European Commission, 2019). So, from an EU internal market perspective the threat from unlicensed medicines has subsided for the moment or counterfeiters have found a very novel way round customs controls.

International police operations can also provide insight into activities of organised criminal gangs in the unlicensed medicines black market. The annual EUROPOL MISMED operation is a Europe wide crackdown on the illegal trade of falsified medicines. In 2020 the week long operation MISMED III operation led to the arrest of 165 individuals, the seizure of 36 million doses of medicine to a retail value of €7.9m. In three years EUROPOL's MISMED program has led to the arrest of 600 suspects and the seizure of €0.5bn of counterfeit medicines. (Europol, 2020) A wider international net is spread through the global INTERPOL police network. Operation Pangea has been running since 2008 and has led to the seizure of more than 105 million units of medicine and the arrest of 3,000 suspects.

As a super-national entity, the EU has a commitment to protecting its external borders while at the same time promoting the free movement of goods and intra-national trade within the community. Medicines are often legally, relabelled for sale in different member state markets. For example, a product that was originally labelled for the German market can be legally re-labelled under license for sales in another market. Parallel market relabelling operation may also take medicines from outside the EU for remarketing in another EU member State. While this free movement of goods is accepted the activity is seen as susceptible to infiltration or abuse by criminals. The European falsified medicines directive demand specific measures, including serialisation, to control parallel trade. In the U.S. parallel trade is also treated as a susceptible point of entry for illegal medicines into the supply chain. (Liang, 2006)

Another phenomenon in the trade of falsified medicines, involving customs controls, is the trend towards using methods of trans-shipments and free ports. This is where unlicensed medicines are imported from a country with high standards of compliance before being routed to their final market. For example, a batch of counterfeit medicines manufactured in Pakistan, bound for the market in Ireland, might first be routed through a shell company and

a port in the U.S. of Japan. Customs authorities in Ireland would be less suspecting of material coming from these destinations than other higher risk countries. This method helps criminals get around the risk assessment procedures of local customs agencies. (European Commission, 2005)

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 use 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 effected 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 EU. 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 taken into account (EUIPO and OECD, 2019)

Along with financial cost the EUIPO/OECD report also highlights the human cost of fake medicines. Between 72,000 and 169,000 children die annually from pneumonia having taken substandard antibiotics. The report cites Singapore, Hong Kong and Singapore as major hubs for fake drugs. This is validated by the EU customs seizures reports previously discussed. The unscrupulousness of the criminals that falsify life-saving medicines was already highlighted by WHO reports. The EUIPO/OECD report gives more detail on the types of medicines that have been counterfeited. See Figure 3.

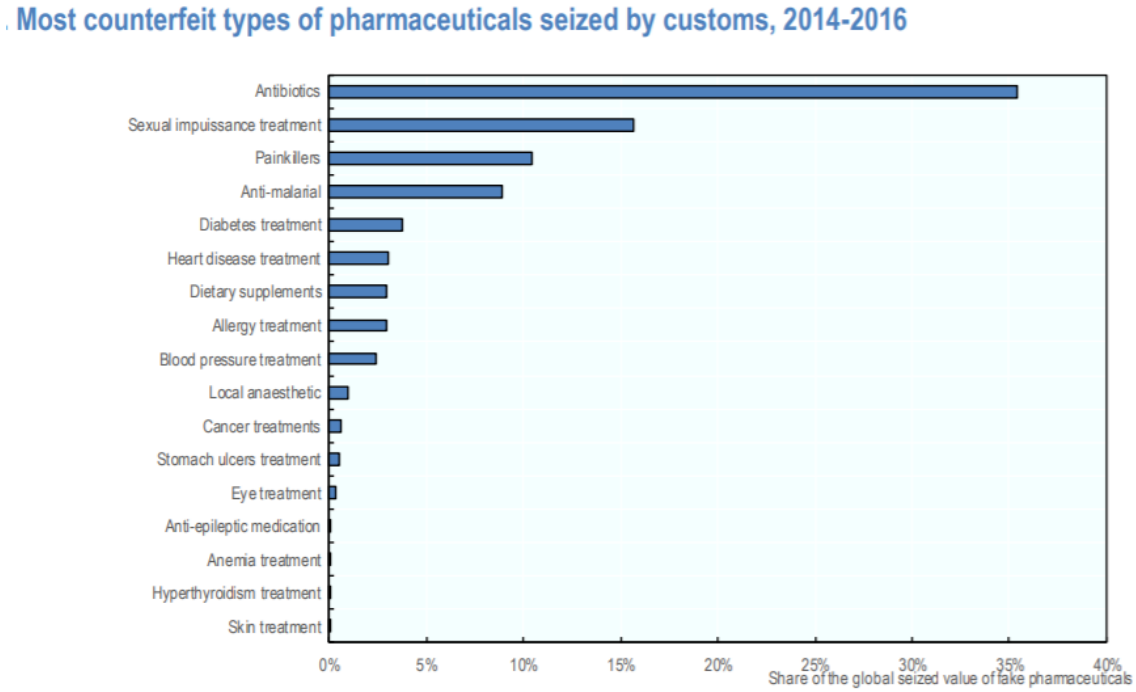


Figure 3. Most Counterfeit medicines (Pharmaceutical Security Institute, 2020)

The EUIPO report references the work of the Pharmaceutical Security Institute (PSI). The PSI gathers incident data privately from pharmaceutical companies. Pharmaceutical companies may become aware that their products have been counterfeited but may not wish to publicly highlight these incidents. The PSI gathers information directly from pharma companies where product has been stolen, illegally diverted, or discovered to be counterfeit. PSI reporting highlights that incidents of product falsification continue to grow at a pace. The PSI reported 5,081 pharmaceutical crime incidents in 2019. This was up 15% on 2018 and is a 69% increase on 2014 figures. These numbers are in contract to the trend in the European Union, as outlined in the annual EU customs seizure reports. The PSI number refer to global incidents

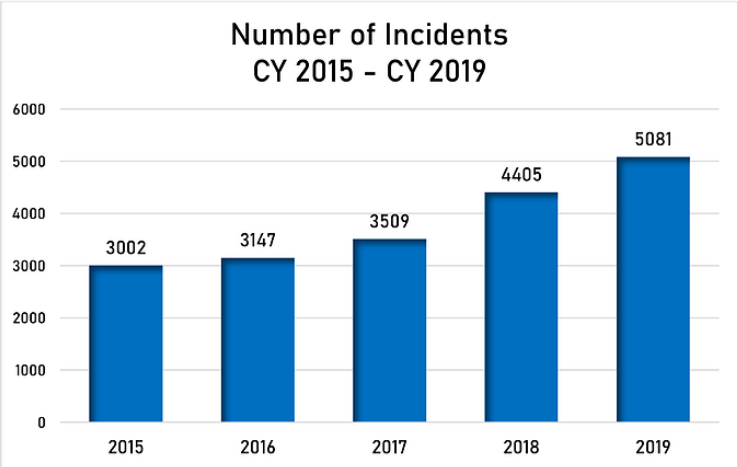


Figure 4. Counterfeit drugs global incidents (Pharmaceutical Security Institute, 2020)

7.5 e-commerce

The CMPI report, discussed previously is also referenced in a report from ASOP – The Alliance for Safe Online Pharmacy (ASOP, 2017) The availability of counterfeit medicines for sale via the internet is referenced as a major concern for governments and regulators. The 2017 ASOP report makes a number of assessments on the scale of the counterfeit drug market in Europe. Based on extrapolations from INTERPOL drug seizures during their operation Pangea, ASOP calculated the value of the counterfeit medicines market in Europe was estimated at €365m per annum. This estimate only considers the retail value of the drugs themselves. Other factors should also be taken into account. For example, the loss of revenues and reputational damage to pharma companies, lost taxes to Governments and untreated health costs. Taking these costs into account, ASOP estimates the cost of the online trade in online fake medicines to the European Union member states at between €935m - €3bn per annum.

The European Union must balance the risk posed by illicit online pharmacies with the EU's commitment to open trade and reducing costs to patients and citizens.

The ASOP report refers to a Legiscript survey of the number of illegal websites shutdown in Europe between 2010 and 2012 following EUROPOL operations

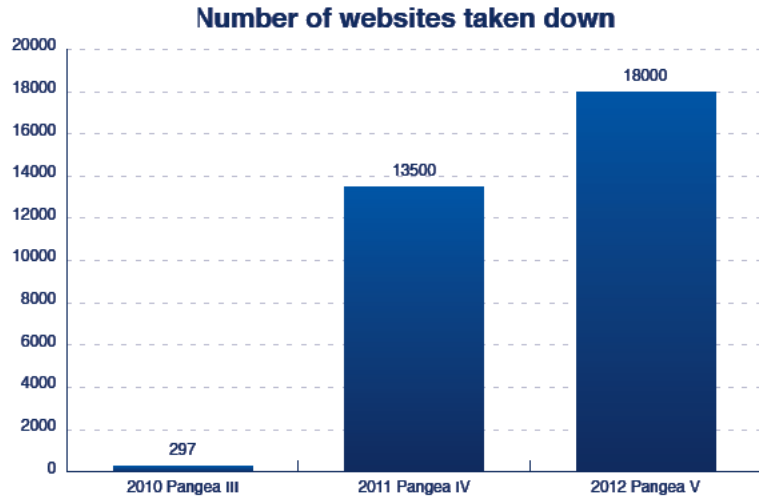


Figure 5 Operation Pangea – Websites shutdown (ASOP, 2017)

The ASOP report highlights an interesting case between Google and the U.S. Dept. of Justice. Google forfeited $500m in a settlement because of revenues from the promotion of illegal online pharmacies in the U.S. dating back to just 2008. The ASOP report point out that if a network of online pharmacies was paying hundreds of millions of dollars in online promotion then this must certainly be a lucrative market. (U.S. Dept of Justice, 2011)

7.6 The impact of falsified and sub-standard medicines on the developing World

When we consider the real damage caused by falsified medicines in the well-regulated and technically advanced Western World, we can imagine the impact these counterfeit products can cause in the developing world. The World Health Organization (WHO) and the World Health Assembly (WHA) recognised the growing threat of counterfeit medicines as far back as 1988. (World Health Assembly, 1988). The WHO started to publish warnings about counterfeit medicines and attempted to raise awareness of the issue. WHO factsheet No. 275 indicated 10% of medicines in the developing World were substandard or falsified. (WHO, 2003).

The WHO Factsheet offered evidence of the devastating effects of counterfeit medicines in developing countries. One case involved a breakout of meningitis in Nigeria in 1995. Médecins San Frontier staff noticed that vaccine medicines were difficult to reconstitute and contained foreign particles. After contacting the vaccine manufactures it was confirmed that the vaccines were counterfeit. 2,500 people died because of these fake drugs (Pécoul *et al.*, 1999)

Another case mentioned in the WHO factsheet relates to an investigation into critical anti-malarial drugs in South East Asia. Nearly 40% of drugs purchased from stores contained no active ingredient. (Newton *et al.*, 2001). While counterfeit medicines represented far less than 1% of the market in wealthy countries, these drugs were primarily used for lifestyle applications (hormones, steroids, antihistamines). In the developing World, counterfeit medicines are often unwittingly purchased to treat life threatening diseases such as HIV, Malaria and bacterial infections.

In 2011, more than 200 patients died after they were given counterfeit heart medication in Lahore, Pakistan. Over 1,000 people became seriously ill because of the treatment. Symptoms included bleeding from the mouth and gastrointestinal tract, dark marks ion the patients' skin and very low levels of white blood cells. (WHO, 2013)

7.7 Technology choices and patent trolls

In the period 2000 to 2005, the FDA seemed to favour Radio Frequency Identification (RFID) as a probable technology to offer a track and trace solution to protect the legitimate medicines supply chain (Ault, 2004). RFID Ultra High Frequency (UHF) is a passive micro circuit that can be stimulated to provide information when scanned. A number of drug companies ran trials using RFID tags on pharmaceutical packaging. Pfizer trialled RFID tags on its Viagra medicines and reported positive results (Thomas, 2006b). Glaxo SmithKline also experimented with RFID technology (Thomas, 2006a). In 2006, Congressman Dan Burton proposed the "Reducing Fraudulent and Imitation Drugs Act of 2006". This Act would have stipulated the use of RFID technology on pharmaceutical packaging (Burton, 2006). The bill did not make it through the legislative agenda of the 109th Congress. The WHO also referenced RFID technology as a technical solution to counteract falsified medicines (WHO, 2007). The European Medicines Agency also investigated the use of RFID technology. By 2011, the European Commission had already issued a directive that a system would be developed to uniquely identify each pack of medicine manufactured and dispensed. At that point however the European Commission had not yet stipulated the exact mechanism for track and trace technology. Three types of technology were considered; RFID, Linear barcode and 2D barcodes (Irish Medicines Board, 2011). The European Commission started a consultation process with industry stakeholders to assess the merits of the technology options (European Commission HEALTH AND CONSUMERS DIRECTORATE-GENERAL, 2011).

A pharmaceutical track and trace system must hold a lot of data on the drug label: country of origin ID, Manufacturers ID, National Drug Code, Product type, a serial number, lot number and expiry date. Hence the references to the use of RFID technology in the literature from 2000 to 2007. There was however another type of data capture technology called the 2D data matrix code. The 2D Data Matrix code mentioned in the 2010 FDA guidance is a type of printed code that can hold up to 2335 alpha numerical characters. The 2D data matrix code was invented in 1953 by Jerome Lemelson. As a data carrying technology the 2D data matrix code was very suitable for serialisation. The 2D matrix code could carry a large amount of alpha-numeric data, it was cost effective and compatible with existing print and bar code reading systems. However, the technology was subject to patent protection and the Lemelson

foundation was actively enforcing patent rights and collecting hundreds of millions of dollars in licensing fees from large corporations for the use of the technology. Given the commercial nature of the technology regulators could not recommend the 2D Matrix labelling method in the early 2000s (Hansen, 2004).

In 1999 the machine vision companies Cognex and Symbol sued the Lemelson foundation and in 2004 won their legal battle. This opened the use of 2D Data matrix technology for industrial track and trace processes including the pharmaceutical industry. In 2006 the International Standards Organization (ISO) published ISO16022 as the international standard for the use of 2D datamatrix codes (ISO, 2006, p.16). The ISO also published a standard on how to grade the print quality of 2D Data matrix codes (ISO, 2004, p.15)

The availability of 2D data matrix codes was quickly embraced by the pharmaceutical industry. In 2007 the French pharmaceutical regulator AFSSAPS (Agence française de sécurité sanitaire des produits de santé) launched a program to replace pharma barcodes with 2D data matrix codes, as a traceability and verification system (Club Inter Pharmatique, 2007).

7.8 International standardisation and serialisation

By the mid 2000's both the FDA and the EMA recognised the need to take action to counteract the threat posed by unlicensed medicines. Regulatory authorities recognised the growth in the sale of unlicensed and substandard medicines on the internet, the infiltration of fake drugs into legitimate pharmaceutical supply chains and the reputational damage caused by dangerous counterfeit medicines in developing countries. In 2003, the then FDA Director Mark McLellan launched a counterfeit medicines task force to come up with new ways to thwart criminal activity in illegal medicines. (outsourcing-pharma.com, 2003) Part of the remit of the taskforce was to identify new technologies that could be used in the fight against illegal medicines. An interim report was published in 2004 that detailed the Task Force's consultation process with manufacturers, wholesalers, pharmacists, medical practitioners, and technology providers. The report detailed how the task force had held a series of public meetings. There were 72 presentations made at these meetings and 54 exhibits from various technology providers (FDA, 2004).

The European Commission adopted a very similar approach to their counterparts in the U.S. on the development of a technology response to the threat of counterfeit medicines. Like the FDA the European Commission sought a response to various policy options from industry stakeholders(European Commission HEALTH AND CONSUMERS DIRECTORATE-GENERAL, 2011) . The responses from the industry were then collated in an impact assessment report. There were important responses from industry stakeholders in Europe to the European Commission's request for submissions. The European Federation of Pharmaceutical Industry Associations EFPIA submitted a response that supported the use of 2D data matrix codes (EFPIA, 2012). The EFPIA also submitted a joint paper with GS1 outlining a common approach to using GS1 standards, in particular the GTIN number, in the European Falsified Medicines framework (EFPIA and GS1 AISBL, 2012). The EFPIA had originally endorsed the use of a 2D Matrix based tracking system in 2006 (European Medicines Verification and System (EMVS) Alliance, 2017). The EFPIA was also involved in another submission to the European Commission as part of a consortium along with the IFPMA (International Federation of Pharmaceutical Manufacturing Associations) and the PhRMA (Pharmaceutical Research based Manufacturing Association) (IFPMA *et al.*, 2013). The consortium report again highlighted the need for the European falsified medicine policy to be based on international standards, citing GS1's data matrix code as a preferred standard for track and trace coding. The report also highlighted expected regulation in Belgium, California, Brazil, China, India and other countries. The IFPMA, EFPIA and PhRMA submission highlighted the hardware and software costs of serialisation. They urged the European Commission to adopt an approach based on international standards that would allow manufacturers to use their investment in serialisation not just for the European market but for other international markets as well. There were also submissions from the European Hospital Pharmacists Association (EAHP) which again urged the European Commission to adopt international standards based on GS1 coding standards (EAHP, 2020).

In another stakeholder submission, the European Consumer Organisation (BEUC) also supported the use of the 2D matrix codes. The BEUC considered that the use of 2D Matrix codes would have the least impact on the eventual cost to the consumer. The BEUC also supported a harmonised regulatory approach across all member states in order to minimise the cost to manufacturers and therefore to any onward cost to consumers (BEUC, 2012).

During the period of policy development, it was clear that both the U.S. and European regulators were actively watching each other's progress to align as closely as possible in terms of anti-counterfeiting mechanisms. Both regulators looked to the GS1 standards organisation when shaping guidance and legislation. GS1 is a not for profit organisation that develops and coordinates barcoding standards. GS1 operates in 112 countries, it has 1.5 million member companies its barcodes and other data recording methods are used in over 6 billion transactions daily (GS1 Ireland, 2019, p.1). The FDA guidance document refers to the importance of international standardisation in the formation of track and trace systems. The FDA ensured that the SNI system was compatible with the GS1 Standards. While the FDA guidance did not obligate manufacturers to use the format laid out in GS1 standards the format suggested by the FDA was compatible with the GS1 organization. The Healthcare User Group (HUG) also started to focus on the use of data matrix codes (GS1 AISBL, 2007). The GS1 was uniquely positioned to garner interest from manufacturers, logistics providers, retail pharmacists and regulators on the use of 2D data matrix codes to track and trace drug products. GS1 also operated globally and could ensure good communication on standards between stakeholders. GS1 highlighted the small print size of 2D data matrix codes as a distinct advantage for the technology (GS1 AISBL, 2013, p.1)

In addition to standardised 2D data matrix codes, GS1 also offered a standard for synchronising data exchanges; Global Data Sharing Network (GDSN). This standard would become important as a guide to the development of data exchanges mechanisms for serialised codes on drug packages. A 2012 McKinsey report on the use of standardised tracking systems, including GS1's GDSN exchange pointed to a healthcare supply chain that connected patients, healthcare workers, medicines and medical devices in a seamless continuum of data (Ebel *et al.*, 2012). In reality, regulators tried to provide for as much alignment as possible between various jurisdictions, but differences inevitably occurred.

7.9 The expected costs of serialisation

The EFPIA response to European Commission on the Falsified Medicine Directive included an estimation on the expected costs of implementation for manufacturers. The EFPIA report referenced a total annual cost to the pharmaceutical industry of €125m for serialisation. This cost included all aspects of the pharmaceutical supply chain from manufacturing, to distribution and dispensing. No detail is provided on this cost in the submission. The EFPIA report also cites a cost of 1.6 cent per pack of medicine and an annual cost to a large manufacturer of €8m per annum. 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 published the correspondence from industry associations, pharmacist representative bodies, health insurers, wholesalers and manufacturers. In total there were 100 stakeholder responses from industry. While some of the submissions from industry stakeholders, such as the submissions from Pfizer and Amgen refer to the cost of serialisation none mention an impact on the operational efficiency of manufacturing sites.

Of the 100 submissions to the European Commission in the consultation process no consideration was given to a potential impact on manufacturing efficiency and therefore a potential impact on the availability of medicines (EUROPEAN COMMISSION Enterprise + Industry, 2008).

In the final European Commission's impact report on the falsified medicines directive there is also no reference to any possible impact on operational efficiencies. The report does give detail on operational costs. The report estimates that once off costs for serialisation technology would come to €150,000 per pack lines. 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 IT systems to manage the flow of serialised data. The final report estimated that printing and packing of serialised codes would cost 2 cent per pack in the first five years. Falling to a half a cent per pack after 5 years, presumably due the depreciation of equipment. These costs are based on the cost of consumable materials and labour. There is no consideration of the impact on productivity. With 14.85bn packs of prescription medicines traded annually in the EU, 2 cents

per pack equates to an industry cost of €297m per annum just to print and check serialisation codes on European pack lines (COMMISSION OF THE EUROPEAN COMMUNITIES, 2008b).

In the U.S. the FDA did not directly carry out a similar impact report, however there were a number of indirect reports that did assess the potential impacts of serialisation processes on the industry. The Pew Healthcare foundation published comprehensive research from Forrester Research that estimated the costs associated with serialisation. The Pew Healthcare report, based on estimates from both pharma companies and vendors, set the average cost to serialise 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 cost was a multiple of the European Commission's estimates. The report does highlight additional labour costs of $291,000 per annum, per pack line. There is no reference to an impact on operational efficiency in the report (Pew Foundation and Booz Allen Hamilton, 2014). The report stated that there was no public analysis available on the costs associated with the implementation of serialisation at the time of publication.

The U.S. Center for Disease Control (CDC) did publish an impact assessment report on 2D data matrix code printing on the vaccines supply chain. 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. Regulations stipulated that manufacturers achieve a minimum ISO grade C for printed labels. 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. Along with the complexity of the 2D codes, the FDA stipulated that manufacturers would still be expected to print linear barcodes on packaging, thus increasing the risk of printing errors (Center for Drug Evaluation and Research, 2018). Again, the CDC impact report contained no reference on serialisation's potential impact on operational efficiency.

7.10 Manufacturing Efficiency

In manufacturing environments operational efficiency is often measured using the OEE method (Overall equipment Effectiveness). The OEE 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 OEE. These are known as the big losses.

(i) Equipment failure/breakdown losses
(ii) Setup/adjustment time
(iii) Idling and minor stop losses
(iv) Reduced line speed
(v) Reduced yield until machines stabilise
(vi) Quality

The OEE calculation provides a common standard to determine production efficiency in different manufacturing sites and industrial sectors (de Ron and Rooda, 2006). OEE is made up of three elements (i) Performance, (ii) availability (iii) quality. Performance is a measurement of line speed. 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 is the measurement of the percentage of good quality products produced from the total. The OEE is calculated as a composite of all three measurements.

OEE % = % Performance X % Availability X % Quality

Serialisation has the potential to affect the three measures making up the OEE calculation. . We have already discussed the 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. Line availability may be affected by the time it takes for operators to setup serialisation data, clear down unused serialised codes and by the stoppages caused by poor quality print.

While there was an absence of comments on pack line efficiency in the impact reports by the CDC and the European Commission, there was some industry realisation for the potential of a negative impact on OEE. Rotunna et al commented that "due to the highlighted changes on the process operations, there could be also an impact on the overall equipment effectiveness (OEE) of the production line. The continuous data exchange between different components, synchronization, and the necessity of waiting for data valid signals may result in overall line speed reduction, with a consequent loss in terms of performance efficiency" (Rotunno *et al.*, 2014). The Rotunna article did not quantify the impact on pack line efficiency. A 2017 report from Pharma Logistics IQ also cited efficiency related costs but these were also unquantified.

The Serialization Playbook published by Healthcare Packaging magazine did estimate the negative OEE impact at between 8% to 10% post implementation. The playbook estimated that OEE would recover to a point 4% lower than pre serialisation (Rodgers, 2014). This range of OEE 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. However, losses of up to 30% were observed during the ramp up period after implementation (Ozkaya *et al.*, 2017). The article also made the point that operators would need training and experience so as to maximise efficiency post serialisation. The International Society of Pharmaceutical Engineers (ISPE) published an article on OEE losses due to serialisation implementation. See Figure 6

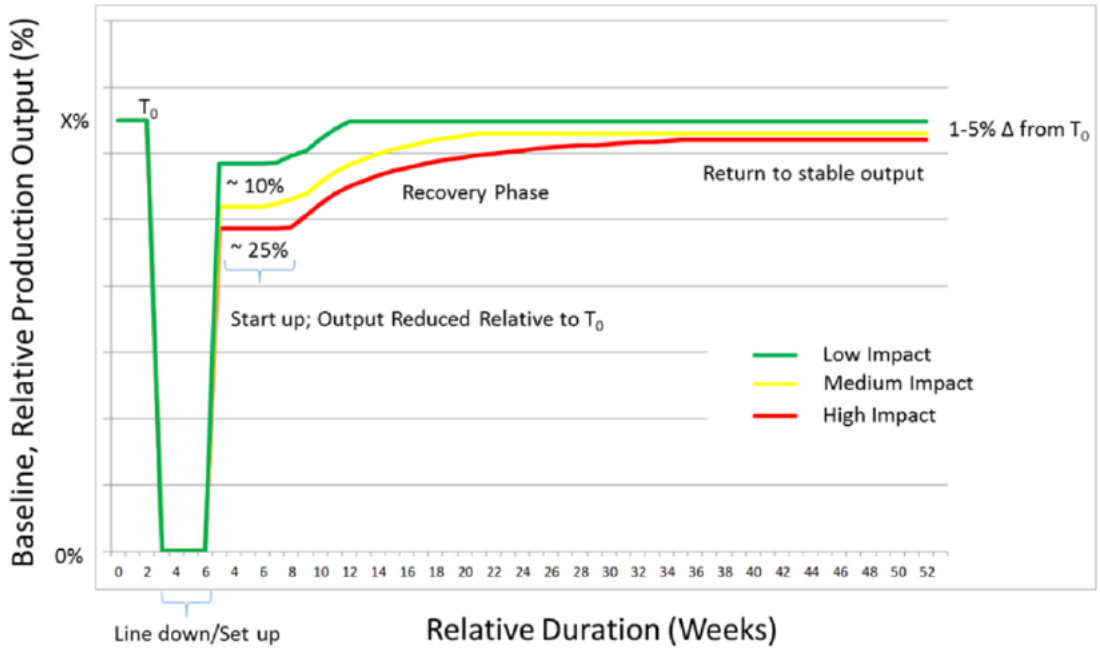


Figure 6 (Penfold, 2018)

The ISPE article indicated losses of between 10% to 25% for up to 2 months post serialisation implementation. Lines may recover to a position 1% to 5% lower than the original OEE position after about six months (Penfold, 2018). In a discussion with the author of the article, Alfred Penfold, it was determined that these calculations were based on a combination of the Healthcare Packaging serialisation playbook (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 OEE impact claims in the ISPE article. The industry sources contributing to the ISPE article would have been close to global serialisation roll-out programs.

One of the advantages of the 2D Matrix Codes (DMC) used for serialisation is that they are forgiving from an operational perspective. The DMC is readable from any orientation. The codes have built in error correction that allows a printed code with up to 30% degradation in print quality to still be effectively read. From an OEE quality factor perspective the 2D data matrix codes help maximise OEE (GS1 AISBL, 2013).

7.11 Planned downtime productivity and Equipment efficiency

The Harvard Business Review defines productivity as “the number of labor hours required to accomplish a given task, when compared with the standard in that industry or setting.” A productivity gain is when a manufacturing site manages to produce more with the same resources, compared to peer companies i.e. doing more with the same resources. The same publication defines efficiency on the other hand as “doing the same with less. Companies most often improve labor efficiency by finding ways to reduce the number of labor hours required to produce the same level of output” (Mankins, 2017) So efficiency can be described as doing more output with less resources while productivity is doing more with the same resources. The serialisation implementation process is not a single event. Software and hardware need to evolve to meet regulatory and market requirements. As new regulations are released in different markets, manufacturers must adopt their serialisation systems to meet these market demands. Figure 11 outlines the release of track and trace regulations in different markets over the last decade. From figure 11 we can see that international regulations are constantly evolving. As regulations evolve so must the software and hardware on packaging lines.

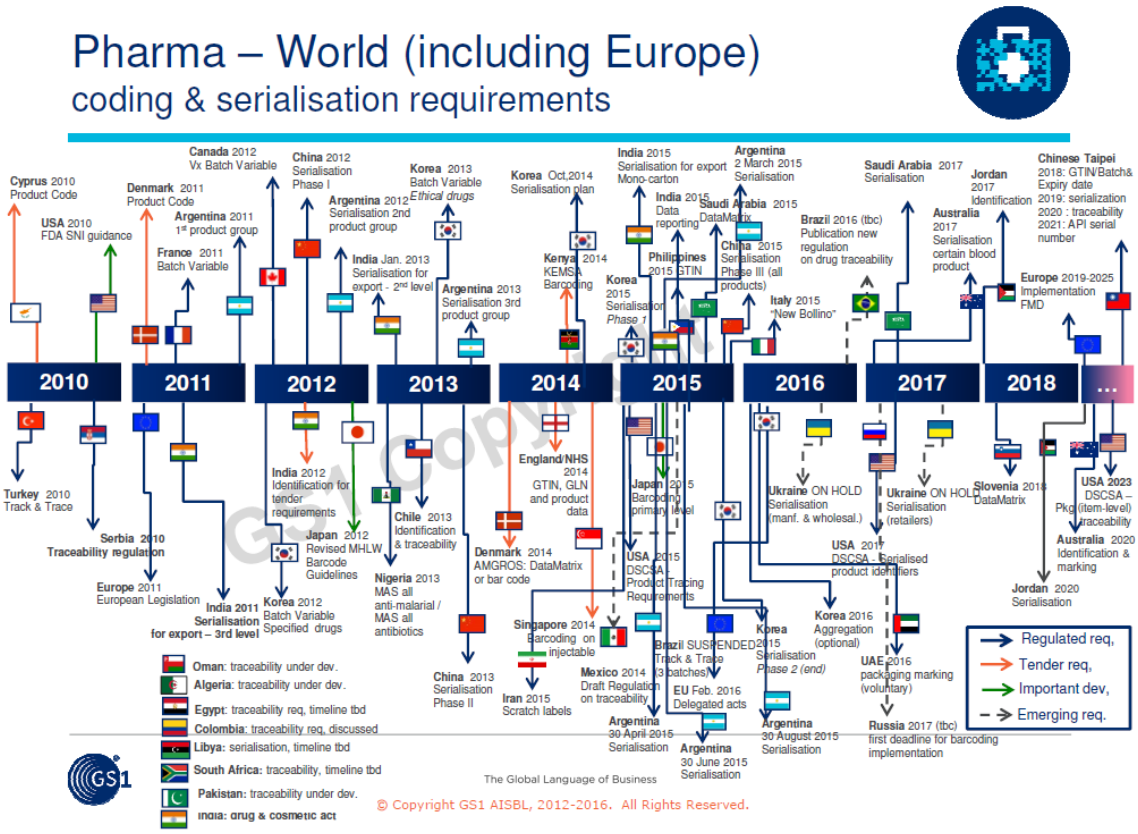


Figure 7 (GS1 AIBL, 2016)

Each time a serialisation system is updated to meet these regulatory requirements the packaging line must be stopped. These stoppages effect the productivity of the manufacturing site. Updates to serialisation equipment are classified as planned maintenance and do not affect the availability measures in OEE. 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. Increases in the COGs are ultimately reflected in the price patients pay for healthcare.

Along with productivity measurements Bragli et al have proposed a modification to the OEE calculation to account for the loss of availability due to planned maintenance events. The OEEM measurement uses the standard OEE measurement and multiples by a factor *Apm*, which is the loss of availability due to planned maintenance (Braglia *et al.*, 2009).

$$OEE = 0EEMxApm$$

Another alternative measure to OEE is the Equipment Effectiveness rate (***E***) proposed by de Ron and Rooda (de Ron and Rooda, 2006). The equipment effectiveness ***E*** rate has three factors similar to OEE; Yield Y, Rate R and Availability A.

Equipment Effectiveness ***E*** = ***A*** x ***R*** x ***Y***

The calculation of the Availability factor ***A*** is interesting in terms of the discussion on the impact of serialisation. In the original work by Seiichi Nakajima on Total Productive Maintenance (TPM) the availability factor was calculated by considering the time available per day less the planned down time. The OEE standard published by SEMI uses total available time i.e. 24 hrs per day for its availability measurement. De Groote defined available time as planned production time less unplanned downtime (De Groote, 1995).

Availability indicator A:

$$\frac{\text{Planned production time} - \text{Unplanned downtime}}{\text{Planned production time}}$$

Figure 8 (de Ron and Rooda, 2006)

The SEMI standards on Reliability, Availability and Maintenance provide a comprehensive consideration of availability states in a production environment. See Figure 9.

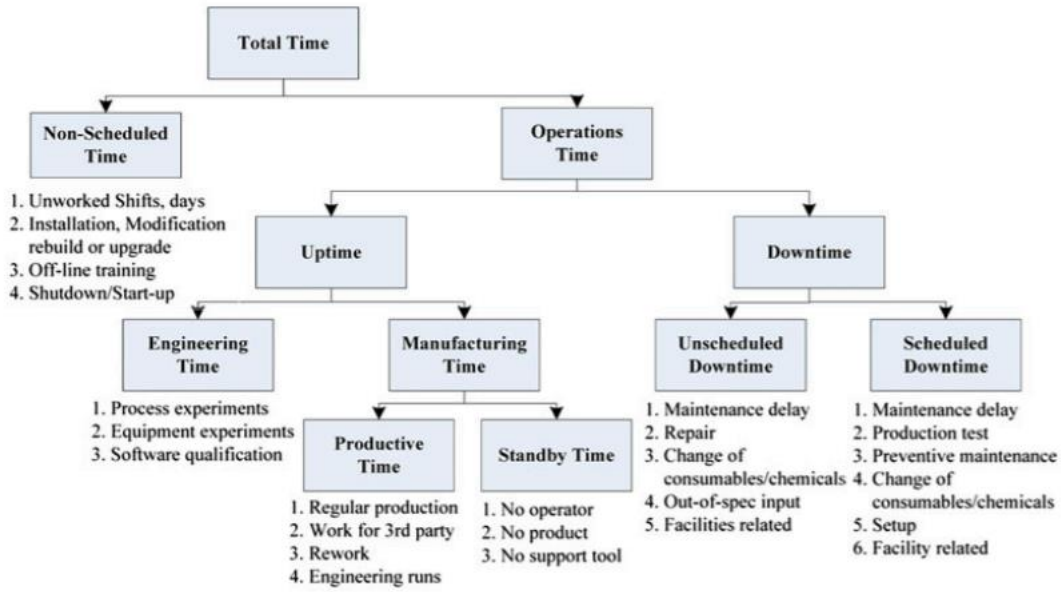
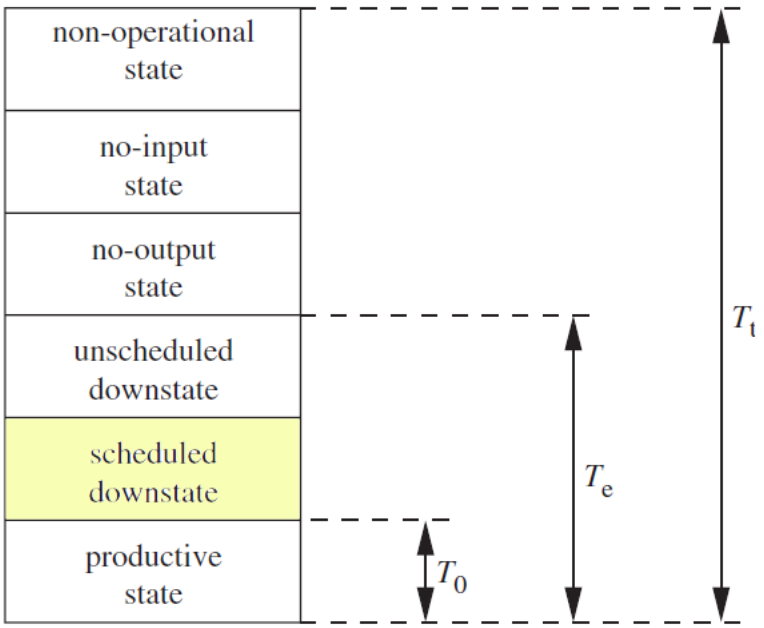


Figure 9 (SEMI, 2012)

De Ron and Rood further categorise the time given to different machine states. Availability factor ***A*** is calculated by breaking down the state of equipment into six categories: Non-operational state, no-input state, no-output state, unscheduled downstate, scheduled downstate, productive state. This categorisation is based on the E10 standard for Reliability, Availability and Maintenance (RAM) published by the Semiconductor Equipment and Materials International SEMI (SEMI, 2012).

The availability factor calculation for ***E*** focuses on the last three categories: unscheduled downstate, scheduled downstate, productive state. The availability factor ***A*** is a measure of the environment in which the machine operates. The first three categories of state (non-operational, no-input, no-output) are not seen as being under the influence of machine operations. By focusing on those factors that relate directly to equipment the Equipment Efficiency factor ***E*** is a truer reflection on the equipment's impact on productivity.



Equipment states.

Figure 10 (de Ron and Rooda, 2006)

In the Rooda and de Ron model Availability factor ***A*** is calculated as the follows.

$$A = \frac{T_0}{T_e}.$$

Where, ***Te*** is the Effective Time and ***T0*** is the Productive time.

As serialisation processes evolve with new regulatory demands how is the time required to update and maintain systems accounted for? If pack lines become unavailable due to updates

in pack line software and systems this may not be captured in an OEE measurement. However it may be captured in an Equipment Effectiveness E or OEEM measurement. ***E*** and OEEM calculations consider the effect of Planned Maintenance on Equipment Effectiveness. Planned maintenance may be used in pharmaceutical sites to mask some of the productivity impacts caused by the requirement to update serialisation equipment. Looking at SEMI breakdowns on Operations and Non-Scheduled time in Figure 9, how do pharmaceutical companies categorise pack line and other serialisation update requirements?

7.12 The OPEX wave in pharma

OEE, OEEM and *E* measurements are part of the operational excellence framework (OPEX). Operation excellence includes Total Productive Maintenance (TPM), Total Quality Maintenance (TQM), Just in Time (JIT) and Effective Management Systems (EMS). The term operational excellence was first discussed by Hayes and Wheelwright in 1984 in their book "Restoring our competitive advantage" (Hayes and Wheelwright, 1984). The concepts associated with the operational excellence grew out of the methodologies adopted by Toyota and other Japanese manufacturers. These concepts were later adopted across a wide range of industry sectors. The pharmaceutical industry was a late starter when it came to operational excellence. This was evident in the high levels of raw materials and finished inventory carried by the pharmaceutical sector compared to other industries (Spector, 2018). Other sectors such as automotive, electronics and food embraced operational excellence techniques in the 1970's and '80's, most pharmaceutical companies did not start their operational excellence journey until the turn of this century (Friedli *et al.*, 2013). The University of St. Gallen in Switzerland has led research into operational excellence in the pharmaceutical industry. The university benchmarks the industry in terms of operational excellence and OEE. See Figure 11.

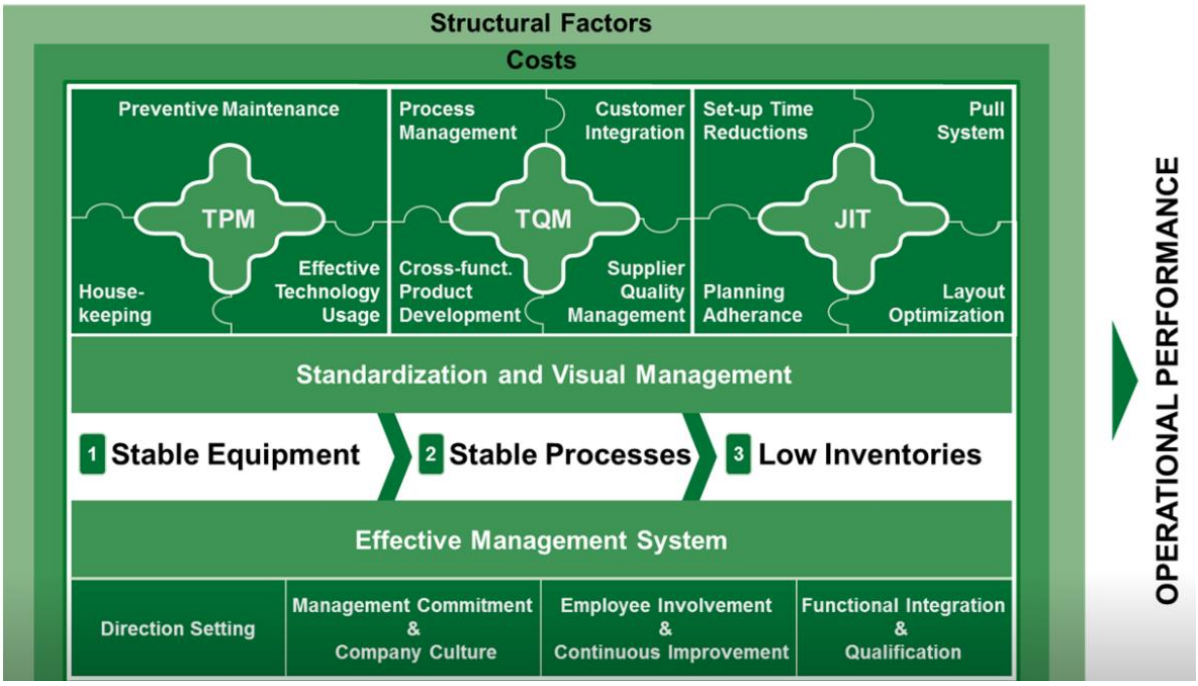


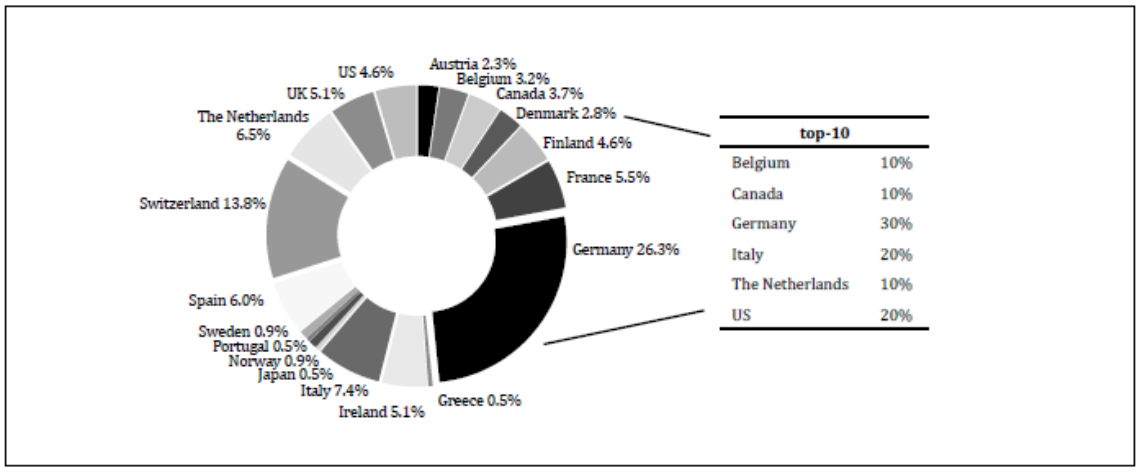
Figure 11 (St. Gallen University, 2020)

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 provided pharmaceutical companies with a "burning platform" to initiate improvements (Schonberger, 2007). 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 started to quickly erode once drugs came off patent. To compete in markets not protected by patents, manufacturers needed to adopt lean manufacturing techniques (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 being frozen and not open to improvement (Friedli *et al.*, 2013). In the mid 2000's a series of 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 focusing on quality control and

stabilisation programs for the control of manufacturing processes, pharma companies now moved to a new phase of trying to systematically improve their organizations and processes.

The adoption of operational excellence techniques by the pharmaceutical industry since the 2000's led to substantial improvement in OEE and other key performance. Figure 17 from the St. Gallen benchmarking report outlines the improvements in OEE by the pharmaceutical company participants between 2006 and 2012. The report cites a 53% gain in OEE performance. Compared to other industries however, the pharmaceutical sector still had a long way to go. Figure 18 compares the OEE ratings in the food industry to that of the pharmaceutical industry. In 2007 the average OEE in a best in class of food processing operation was 24% ahead of the average OEE in a best in class pharmaceutical company. Irish pharmaceutical companies were in the vanguard of the Opex revolution. In a 2015 analysis of global " best in class" pharmaceutical sites, Ireland had 5% of the total (Bellm, 2015). See Figure 16



Geographic distribution of the advanced and top-10 sample

Figure 12 (Bellm, 2015)

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

At the same time pharmaceutical companies were starting to make strides in OEE gains they also started to focus on other operational benchmarks such as raw material inventories, demand-based manufacturing, and increased stock turns for finished goods.

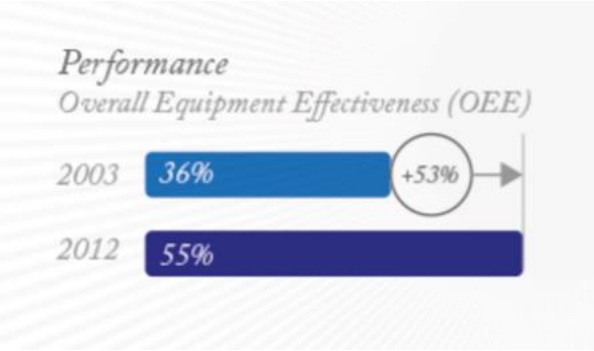


Figure 13 Operational Equipment Effectiveness gains (Casali, 2019)

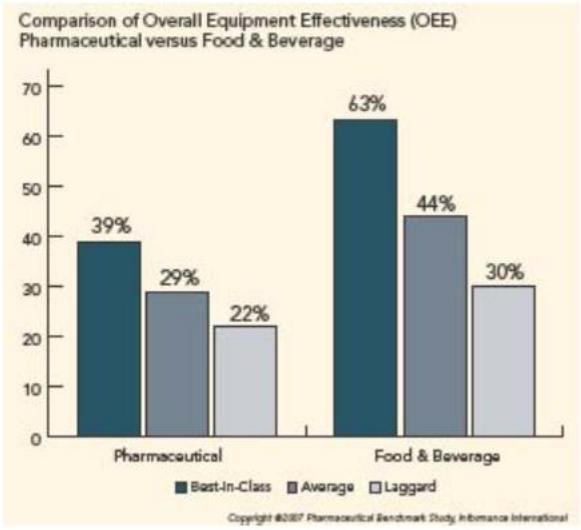


Figure 14 *(Rodgers, 2014)*

Some of the negative impacts on OEE identified in the literature and previously discussed, were exacerbated by this drive toward lean manufacturing and operational excellence. Any delay in setting up serialisation information for a batch during batch changeover impacts availability. The more batches that go through a pack line then the greater the risk of the serialisation label print and check systems causing errors and effecting product quality.

Negative impacts on OEE need to be balanced against some of the positive effects of serialisation implementation. This balance may be influenced by the age of the pack line. 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 opted to replace older pack lines with newer equipment. This capex investment in new equipment may also have brought better line speeds and faster changeover times. Even without replacing older pack lines, the addition of better cameras and printers during a serialisation installation may improve line performance. One vendor reported that a manufactured saved $100,000 USD per annum by replacing manual inspectors with an automated vision system during a serialisation implementation (Pirrera and Jordan, 2014). Another vendor reports that a client started to seriously monitor OEE post serialisation. By working closely with operators the business was able to eliminate waste and increase OEE by 20% (Butschli, 2017).

The pharmaceutical pack line is the epitome of the late stage customisation demanded by lean manufacturing. A medicine does not become a medicine until it is correctly labelled and serialised for a specific market. Any negative or positive impact on OEE or OEEM will affect a manufacturing sites operational efficiency and productivity.

7.13 Pharmaceutical industry productivity

The St. Gallen studies outline the improvements in equipment efficiency in the pharmaceutical industry from 2005 to date. However, during this time period there has been no real improvement in pharmaceutical industry productivity. A key indicator of a manufacturing company's progression in lean manufacturing is its inventory turn. That is the value of the company's stock-on-hand compared to its annual sales. Spector reported that compared to other manufacturing industries, the pharmaceutical sector made little impact on inventory levels in the period 2000 to 2009 (Spector, 2018). Analysis of public company data in the period 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 as a whole, the generic medicines sector being the only exception. See Figure 19.

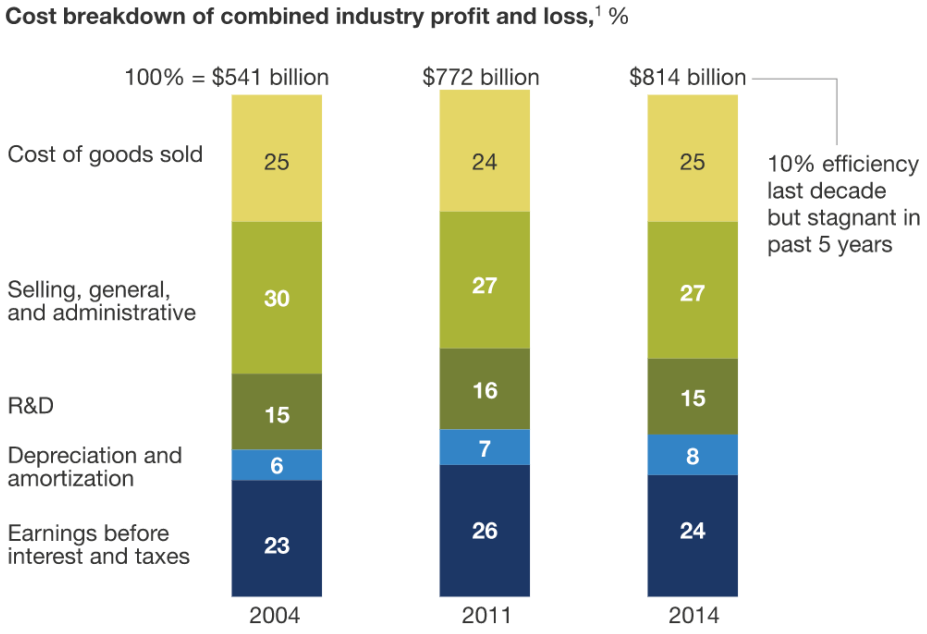


Figure 15 *(Gyurjyan et al., 2017)*

This stagnation in the cost of goods as a percentage of total sales across the pharmaceutical productivity was also identified by Basu et al during the period 2006 to 2008 (Basu *et al.*, 2008). Vernon et al 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 additional margin by manufacturers while any increase in the cost of goods is passed on through higher prices (Vernon *et al.*, 2007). If serialisation processes did effect productivity then this may be reflected in the cost of goods and the price of healthcare for patients. Serialisation processes do not just impact the packaging halls in pharmaceutical companies. A study by GS1 Ireland and industry consultants Enterprise System Partners found that serialisation project teams included representatives from departments such as packaging, automation, engineering, IT, quality, operations, manufacturing, artwork and sales. The Harvard Business Review (HBR) terms this type of cross functional activity as "organizational drag". The HBR reports that companies can lose up to 20% of its productive capacity through structures and processes that consume personnel's time (Mankins, 2017). Do serialisation processes cause organizational drag in manufacturing organisations?

7.14 Gaps in the literature

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 Irish 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. There was little follow up in the literature as to the accuracy of the original expectations outlined in policy maker's impact assessment reports. No literature was found that discussed a detailed impact of serialisation on operational efficiency or productivity. The literature gave some indication that efficiency may increase or decrease because of serialisation but there no clear outcomes were identified. Very little data was available in the literature that discussed serialisation in the Irish context. The literature did not indicate how serialisation processes might have affected pharmaceutical productivity or the cost of goods sold.

8. Research Method

This section outlines the research methods used in the study. The reasoning for the method is discussed along with its advantages and limitations. This purpose of the research method is to determine the the impact of serialisation on the operational efficiency and productivity of Irish pharmaceutical manufacturing sites. The research method for the study had three objectives:

(i) To determine if the costs of serialisation outlined by policy makers and industry representatives in advance of the implementation of serialisation systems was accurate

(ii) To assess the impact of serialisation on operational efficiency by examining measures such as OEE and production line availability

(iii) To assess the impact of serialisation on pharmaceutical site productivity by examining measures such as Cost of Goods Sold (COGS) and per unit cost. Research participants would also be questioned on any correlation between serialisation and operational excellence techniques

The methodology chosen for the study was a mixed method incorporating both qualitative and quantitative tools. A qualitative research approach was included as it allowed subject to be studied in their own surroundings. (Denzin and Lincoln, 2011).

Flyberg emphasises that practical knowledge is superior to theoretical knowledge (Flyvbjerg, 2016). Part of this research is to compare the theoretical projections outlined in the literature at the start of serialisation and to compare these predictions with the practical experience of manufacturing sites.

Engineering based research traditionally uses quantitative methodologies. However qualitative based research methods can provide unique scientific findings that may not be identified by quantitative research alone. In the case of this study, it may be impossible to conduct experiments on the impacts of serialisation on high demand pharmaceutical pack lines. It is possible to interview members of the pharmaceutical community who did conduct such experiments and who did statistical analysis on production lines. The report from the

19th International Conference on Design Engineering asserted that qualitative research could enable engineers to determine findings that were not obtainable by quantitative methods (Lee *et al.*, 2013).

Szajnfarber and Gralla cite two scenarios when qualitative research should be used in engineering studies. The first scenario is when the phenomenon to be studied is new or has not been studied. When a new phenomenon is to be investigated there may be a lack of clarity on what to measure or a lack of sufficient knowledge to make reasonable modelling assumptions. The second scenario when qualitative data may be useful is when it is impossible to replicate a model in a laboratory setting or where the context of the experiment is too important to ignore (Szajnfarber and Gralla, 2017). In this study it would be virtually impossible to get access to a serialisation pack line to determine how serialisation processes impact efficiency and productivity. The wider impacts of serialisation infrastructure on IT systems, databases, communication interfaces, regulatory departments, design and supply chain would also not be adequately considered. Szajnfarber and Gralla describe how qualitative research methods may be used to develop better system understanding and for framing hypotheses and correlations.

Ljungberg and Douglas reported that qualitative research in engineering education was under-utilised. They encouraged researchers to use a qualitative approach in research design so as not to miss a rich source of information (Koro-Ljungberg and Douglas, 2008).

8.1 Semi-structured Interviews using open ended and closed ended questions

Within the framework of qualitative research, the study uses the method of semi structured interview to gain insight on the research question. This format was chosen as it allowed the researcher to ask open ended questions that could elicit a detailed response from interviewees. A study by Hove and Anda cited that semi-structured interviews were increasingly used in engineering research (Hove and Anda, 2005). Their study examined semi-structured interviews with 280 software engineers. The study concluded that in order to be successful semi-structured interviews should be:

(i) carefully planned,
(ii) that the interviewer should have appropriate subject skills
(iii) that there is good interaction between interviewer and interviewee
(iv) and that appropriate tools are used

For the purposes of this study the researcher connected with the interviewees in advance of the semi-structured interview process in order to make them aware of the request for interview and the general topic for discussion. In the course of employment, the researcher developed some understanding of the pharmaceutical packaging sector and of serialisation technology. While not a subject matter expert (SME), the researcher has enough subject knowledge to adequately conduct an interview with SMEs and to ask appropriate follow up questions. The researcher applied software tools such as video conference technology (Microsoft Teams) and Excel to interpret the interview data.

The semi-structured interview process allows the researcher to offer questions and statements and for the interviewee to respond to these in the best way they see fit. Cohen et al described the semi-structured interview: “There is a clear structure, sequence, focus, but the format is open-ended, enabling the respondent to respond in her/his own terms. The semi-structured questionnaire sets the agenda but does not presuppose the nature of the response” (Cohen *et al.*, 2007)

The study uses a questionnaire format with a combination of introductory closed-end questions and open-ended questions. This format was chosen because the open-ended questions used in the semi structured interview allowed for a deeper analysis of the respondents' experience across the range of research questions. The semi structured interview method was suitable for use with a low respondent population. Ireland's exports of fully packaged pharmaceuticals are valued in billions of euros. However, there are less than two dozen sites contributing to most of this value.

The semi structured interview process was also chosen because of the Covid-19 pandemic. Face to face interviews were not feasible due to Government mandated travel restrictions as well as Covid 19 policies adopted by manufacturers. A focus group-based methodology had been considered prior to the pandemic but this was ruled out due to the Covid 19 restrictions

Sherri Jackson summed up the relative advantages and disadvantages of open ended and closed ended questions in research in her book, Research Methods a Modular Approach: "Open-ended questions allow for a greater variety of responses from participants but are difficult to analyze statistically because the data must be coded or reduced in some manner. Closed-ended questions are easy to analyze statistically, but they seriously limit the responses that participants can give. Many researchers prefer to use a Likert-type scale because it's very easy to analyze statistically" (Jackson, 2014)

8.2 Sampling Methods & Population

The HPRA list 127 companies in Ireland with pharmaceutical manufacturing licenses (HPRA, 2020). Of these its estimated that less than 17 sites have machine-based packing lines with serialisation activities. This study interviewed respondents from 11 companies. The survey sample size represents approximately 65% of the pharmaceutical packing sites in Ireland. Questionnaires were sent to the respondents in advance and completed as part of the semi structured interview format using video conference technology. Respondents hold positions in serialisation, project management and operational excellence.

8.3 Instrument & Data Collection

The survey instrument used was a closed and open questionnaire format in a semi-structured interview. The process was not self-administered by the respondent but rather the researcher worked in conjunction with the respondent to complete the questionnaire during the interview process during the video conference session.

The survey method followed Cohen's guidance on the layout of questionnaires. The Cohen method suggest breaking down the questionnaire into three sections:

(i) The first section uses non-threatening factual questions such as position, company profile, number of packing lines etc

(ii) The second section moves to closed questions using multiple choice, scales and yes/no type questions. These answers may require a response based on opinion, attitudes, or views

(iii) The final section focuses on open ended questions that seek longer format information based on the respondent's views, opinions, and experience.

(Cohen *et al.*, 2005)

The questionnaire started with closed questions establishing the respondent's background, their company profile and the profile of their company's pack-line and serialisation operations. Closed ended questions can be completely quickly by the respondent and are easy to code for the researcher. Closed ended question do not differentiate on the basis of respondents' articulateness. This was followed by a series of open questions that encouraged the respondents to consider their responses and to draw on past and present experiences. Badger et al described open ended questions as not multiple-choice questions with multiple correct answers or questions that have a single correct answer. "Rather, open-ended questions address the essential concepts, processes, and skills that go beyond the specifics of instruction to define a subject area. In general, they require complex thinking and yield multiple solutions" (Badger *et al.*, 1992)

The questionnaire and interview questions were circulated to respondents in advance of the semi-structured interview in a PDF format via email. Respondents received the semi-structured interview questions in advance so that respondents could ensure that the

interview met with their company policies and guidelines. The researcher completed the questionnaire during the interview process.

Partly because of Covid 19 restrictions the interview process was conducted using the Microsoft Teams platform. The Zoom video conference platform was also provided as an option. Part of the advantage of the Microsoft Teams platform is that it has inbuilt video recording and transcription available. This allowed a virtual face to face interview while also providing a mechanism to record the interview. Braun et al described how the use of the video conference format has developed for use in qualitative research (Braun *et al.*, 2017). The use of video conferencing software in qualitative research has been facilitated by several factors:

(a) An improvement in the availability and speed of internet access as well as the availability of camera enabled laptops, phones, and tablets
(b) The ease at which video conferences interviews can be arranged in comparison to face to face interview or focus groups when respondents are spread over a large geographical area
(c) An understanding that online methods can complement and potentially improve traditional interview and focus group methods

The video conference format allowed the researcher to build a rapport with the respondent. Respondents had the option not to use the video feature of the software as desired. The video conference instrument allowed the interview to be conducted in the respondents' own space, helping to ensure that the interviewee was comfortable. The video conference format provides researchers with the ability to see non-verbal clues from respondents compared to a traditional phone call. However compared to a face to face interview many non-verbal indicators could be missed (Seitz, 2015). The headshot provided on a video conference call only provide part of the non-verbal indicators available (Cater, 2011). Janghorban et al concluded that the video conference method, Skype (now Microsoft teams) was suitable as an alternative or as a supplementary instrument to interview based qualitative research (Janghorban *et al.*, 2014). Studies by Archibald et al described respondents positive experience using video conference platforms in qualitative research. Respondents cited the convenience, ease of use, security and interactivity of video conference calls. The ability to

share screens was also important to respondents in the Archibald et al study (Archibald *et al.*, 2019).

Given the Covid-19 restrictions some interviews were conducted with the respondents in their homes while others were conducted at their place of work. Sy et al, discussing the use of video conferencing technology as qualitative research tool during the Covid-19 point that while video conferencing enables research to continue while both researcher and respondent have restricted movement that consideration should be given to research design, data collection methods and ethics (Sy *et al.*, 2020).

8.4 Code of Ethics

At the start of the interview process it was stated clearly to interviewees that their confidentiality was assured and that their anonymity would be preserved. An explanation of the steps taken to ensure confidentiality and anonymity during the research process was read out to the respondents as part of the questionnaire at the start of the interview. In order to ensure anonymity participants were not asked for their names or the names of their company during the interview process. Participants were asked in advance of the questionnaire and interview process if any special permissions are required from their employer to participate in the research. None of the companies represented in the research will be identified and no specific information will be sought. Respondents may be asked to indicate the range or category of impact on their operations but not for specific data points.

A method of pseudonymity is used to protect the identity of the participants and their employers. Pseudonyms are used in the preparation of written transcripts from the respondents and in any subsequent documents or publications. Pseudonyms will be adopted as soon as possible within the transcription and analysis phase. Each participant will be assigned a code. The register of codes and names will be held on a written sheet, stored in a locked cabinet. Video recordings made during the interview process will be immediately deleted following transcription and anonymisation. Any printed copies of the transcription will be held in a locked filing cabinet. Soft copies of the transcribed interview will be stored electronically using encryption and password protection.

8.5 Data Analysis

The data received through the questionnaire was manually coded using an Excel Spreadsheet. Each questionnaire and transcription were assigned a number and the details inputted into the spreadsheet. A key word analysis was used on the transcription of the open-ended questions from the questionnaire. A coding frame was used to identify and tabulate key words and recurring themes. Excel was used to generate graphs and tables to represent the data. The frequency of key words and themes was identified and correlations between variable identified.

9. Findings

9.1 Introduction

The researcher interviewed 13 representatives from 11 pharmaceutical companies. The participating companies provided a strong representative sample of the Irish pharmaceutical packing industry. The companies interviewed make up approximately 65% of the major pharmaceutical packing sites in Ireland. The majority of the sites interviewed were large volume sites with 49% of respondents producing over 20 million pharmaceutical packages per annum. 30% of respondents produced over 50 million packs per annum.

The respondents to the survey all had direct experience with serialisation implementation and operations. Respondents held positions in operations, engineering, opex and information technology. 85% of interviewees had over 10 years' experience in the pharmaceutical industry and 60% had greater than 15 years' experience. Participants held positions ranging from global serialisation leaders, local serialisation subject matter experts (SME), director of engineering, capex project managers and opex experts. Each position and discipline brought its own perspective on the research questions.

In total the survey covered the operation of 114 packing lines. Of these pack-lines, two thirds (66%) were serialised and 39% had aggregation capabilities. Of the 76 serialised lines discussed in the survey 45 had aggregation capabilities meaning that 59% of the pack lines discussed had track and trace capabilities. For the purposes of survey and interview the researcher grouped serialisation and aggregation activities together as one process is an extension of the other.

The findings were broken into the following themes:

(i) Serialisation and operational efficiency

(ii) Serialisation and production line availability

(iii) Serialisation and productivity

9.2 Serialisation and operational efficiency

Of the 11 companies and 13 industry professionals that took part in the survey and interview process, all expressed an opinion that the OEE of pack lines was adversely affected by serialisation. Except for one site, all the respondents indicated that OEE was measured in their packing facilities. Only one site had a fully automated OEE system across all its pack lines. Even at this site there was a necessity to produce manual reports from the automated data capture system. Two other sites had one or two pack machines that were capable of measuring OEE automatically, but for the most part these sites still operated on manual OEE data gathering and calculations. 89% of the sites surveyed conducted manual OEE data gathering and calculations. Sites did have plans to move to automatic OEE capture with OSI PI, OEE Systems and Werum mentioned as potential partners for automated OEE data capture.

Most pack-lines discussed in the survey were retrofitted. One participant described serialisation as trying to modify a car while it is still in motion. In 4 of the companies surveyed 100% of their pack lines were retrofitted. In comparison just one company purchased entirely new pack-line equipment for the serialisation project. Most companies needed to interweave the deployment of serialisation processes into existing pack-line operations without disrupting production. The process of retrofitting pack lines for serialisation means a loss of line availability. A line that is unavailable for production due to a serialisation upgrade will have a negative impact on site productivity. New pack lines with inbuilt serialisation systems can be tested and validated at the OEM's premises without affecting existing operations. The survey revealed that the average age of a pack line among participating companies was 11 years. The literature review had mentioned a lifespan of 20 years for a pharmaceutical pack line. This means that over the next 10 years companies will need to replace pack machines resulting in farther availability losses.

Participants were shown the graph in Figure 11 on the predicted impact of serialisation on operational efficiency. Interviewees discussed their experience compared to the experience outlined in the ISPE article.

		Participating company response										
Months	Article %	1	2	3	4	5	6	7	8	9	10	11
1-3	5 -10	n/a	n/a	15	50	15	11	n/a	n/a	n/a	20	30
3-12	3-8	n/a	n/a	12	15	5	5	n/a	n/a	n/a	7	20
>12	1-5	n/a	n/a	10	2	2	3	n/a	n/a	n/a	2	0

Table 2 OEE losses

Table 1 shows that that half of the participating companies could not describe a loss of OEE post serialisation. Even though most companies (90%) indicate that they record OEE only 50% could indicate if serialisation had any impact on efficiency. It may have been that a serialisation SME may not have OEE data readily available. However, in at least two responses, an operational excellence respondent was not able to provide pre and post serialisation data even though the company manually recorded OEE data. This result may indicate that companies had not considered the impact on OEE sufficiently in advance of the serialisation project.

			Company No.					
Month	ISPE Article %	**3**	**4**	**5**	**6**	**9**	**10**	**11**
1-3	5 -10	15	50	15	11	0	20	30
3-12	3-8	12	15	5	5	0	7	20
>12	1-5	10	2	2	3	0	2	0

Table 3 Companies indicating a post serialisation loss in OEE

The average OEE loss reported by the companies surveyed was 2.71%. Two companies reported having no loss in OEE despite reporting additional time spent on line changeovers. Removing these two companies from the data yields an average negative OEE impact of 3.8%. In those companies that did indicate post serialisation OEE measurements, one company did cite a significant loss to OEE. Company # 4 in Table 2 is a high-volume manufacturer. The company reported a 15% loss to OEE in the 90-day period post serialisation. The ISPE report had predicted a maximum loss of just 10%. In the period up to 12 months post serialisation the ISPE report predicted a maximum loss of 5% while this manufacture experienced a loss of

12%. The ISPE article predicts a maximum loss of just 5% after 12 months. This manufacturer continued to see a loss of 10% compared to its pre-serialisation situation. In the period up to 12 months post serialisation the ISPE article had underestimated the losses for this manufacturer by 50%. One year post serialisation the ISPE article had underestimated the losses for this manufacturer by 100%. Perhaps the data from this manufacturer was inadequate? In the interview with this manufacturer it was outlined how the company had taken great care to formalise its OEE measurements in the run up to the serialisation project. The company established a 'level playing field" across all its manufacturing sites to properly define and measure the potential impact of OEE. The company had a global team available to monitor the OEE impact of serialisation. Of all the companies interviewed, the company with the highest reported losses seemed to have the most robust, benchmarked, OEE measurement process. Based on the interview with the participant the researcher would have a high degree of confidence in the OEE losses indicated by this company.

Company # 4 reported that after 12 months its OEE figures were in line with the ISPE article with an OEE loss of just 2%. However, in the 12 month period following the implementation of serialisation the OEE losses reported by the company were significantly higher than those outlined in the ISPE article. Company #4 initial losses 90 days post serialisation were 5 x times that indicated by the ISPE article. In the 3-month-to-12-month period post serialisation losses were double that expected from the ISPE article. Company #5 and #6 were broadly in line with the ISPE article expectations.

Company #1 did not have post serialisation OEE results. However, in interview the company did report that they experience reworks due to serialisation errors about 15 times per year. Reworks involving serialised products are very complex to process. The participant described how each rework takes 4 x staff and 3 x days labour to process. In terms of availability this equates to 45 days lost production on one pack line, per annum or a 18.75% loss in availability if the site operated on a single shift per day. Across the site in question the rework issue equates to a 2% loss of availability across all pack lines. This does not consider the time taken for line setup challenges, additional documentation to complete batches or other errors associated with serialisation. One contributor described the serialisation process as adding between 10 – 15 minutes to each batch setup. However, another serialisation manager at the site described serialisation as currently having zero impact on OEE.

The same company described testing of the data matrix code scan quality every 15 minutes. If a single unit fails, then all product going back to the last positive test must be removed for testing. At a line speed of 100 parts per minute, 1500 products may need to be tested due to a print error on a single package.

Company # 2, which does not measure OEE as key performance indicator (KPI), described a product recall situation because an additional set of characters included in the 2D matrix code did not scan at the distribution centre. This meant that the entire batch need to be reworked. Even if this type of quality errors is infrequent the increased risk posed by the serialisation processes should not be ignored.

Company # 5 described the use of challenge materials to check cameras on the serialisation system. These challenge tests and associated paperwork increase the setup time for each batch.

Company #6 reported that Initially, post serialisation implementation, setup times for serialisation increased to 45 minutes. Over time the serialisation setup time has reduced to 20 minutes per batch. The company described doing approximately 1,000 serialised batches per year. This equates to 333 hours per annum for serialisation batch setup. Across 6 x serialised lines on one shift this equates to a 2.89% OEE loss. This equates to the company reported loss of 3% loss in OEE due to serialisation. However, in addition company #6 also described a loss of line speed due to serialisation of between 5 – 10%.

Company # 10 reported that OEE was impacted by 2% post serialisation. The company described how line speeds needed to be reduced by 10% to 15% to ensure that print quality was acceptable for certain products. This was dependent on the quality of packaging materials. Poorer quality packaging would require a reduction in line speed for inkjet printers to produce acceptable 2D matrix codes. Machine vibrations could impact the ability of laser printers to print correctly. The quality of glue used in tamper evident seals could cause divots and bumps on cartons that would cause print issues. The participant from the company described how serialisation was less forgiving on printers and vision systems than in the period prior to serialisation. The company also described how In Process Control (IPC) checks would identify print errors in the 2D matrix codes. Poor print quality would need to be traced back to the last good unit printed. In the 30 minute period between IPC checks 6,000 units

could be removed from the line for visual inspection or rework. The company also described how setup time for each batch increased by 50% due to serialisation processes. For simple batch changeovers, changeover time went from 30 to 45 minutes. When container sizes were changed the change-over time went from 2.5 hours to 3 hours due to line challenges following line adjustments.

Company # 11 also reported that serialisation processes increased changeover times by 15 to 20 minutes to allow for line vision challenge tests and documentation.

Company # 9 reported that serialisation processes did not impact their OEE. However, the company did report that their line speeds were optimised for packaging quality which may indicated that line speeds were reduced to cope with the demands of effectively printing 2D codes. The company also reported additional batch setup time but no impact on OEE.

Participants cited several factors for improvements in OEE post serialisation. Operator training, the development of subject matter experts and knowledge sharing between pack-line teams all contributed to better pack-line effectiveness. Better operating procedures and software improvements from vendors were also cited as routes to efficiency gains. One high volume site that experienced a high degree of OEE loss went so far as to develop its own ink formulation for the inkjet printers used in serialisation to improve print quality on the data matrix codes.

9.3 Serialisation and line availability

Serialisation should not be as a once-off project. Since the introduction of serialisation by the U.S. and European regulatory authorities there has been a series of upgrades and new regulatory milestones. Besides FDA ana EMA regulations, serialisation hurdles have been provided by Turkey, China, Brazil, Saudi Arabia and Russia. Each new market may have its own requirements and will necessitate serialisation vendors to provide software patches and upgrades. Among the customers surveyed the first serialisation project started in 2011. One company did not start its serialisation project until 2018, just ahead of the European falsified medicines directive deadline in February 2019.

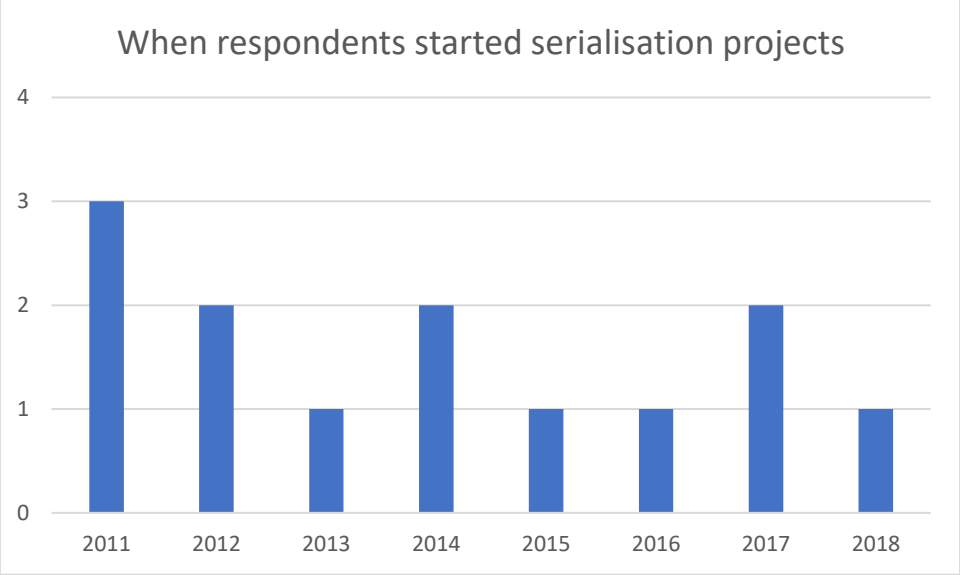


Figure 16 Start of serialisation projects

Serialisation SME's described how they are often challenged by team members in operations, scheduling and opex about the impact of serialisation and aggregation on line availability. The survey asked participants how often serialisation systems needed to be updated. 55% of the companies' surveyed have upgraded their lines for serialisation at least once per year. 85% of participants upgrade lines at least once every eighteen months. In interview participants described how line upgrades take between 2 weeks and six weeks to implement. Major upgrades such as the addition of aggregation capabilities can take between 3 to six months to install. When lines come out of production to undergo these upgrades the loss of availability is not accounted for in OEE calculations. The loss of availability is tagged as planned downtime. Other calculations identified in the literature such as OEEM and Equipment

Effectiveness factor may be used to account this loss of availability. Only one of the companies surveyed used OEEM or Equipment Effectiveness as a measure of line availability. However, three sites did describe other measures used to capture the loss of line availability. These measures included calculations for line utilisation, max capacity Vs actual production and site potential capacity calculations. Company #10 had calculated that taking one pack-line off the production schedule for one week equated to a loss of 570,000 units or a 1.14% loss in annual production capacity. The same company reported that this type of line upgrade was required once per year. Figure 17 below records the frequency at which participants make pack lines unavailable so that upgrade work can be carried out.

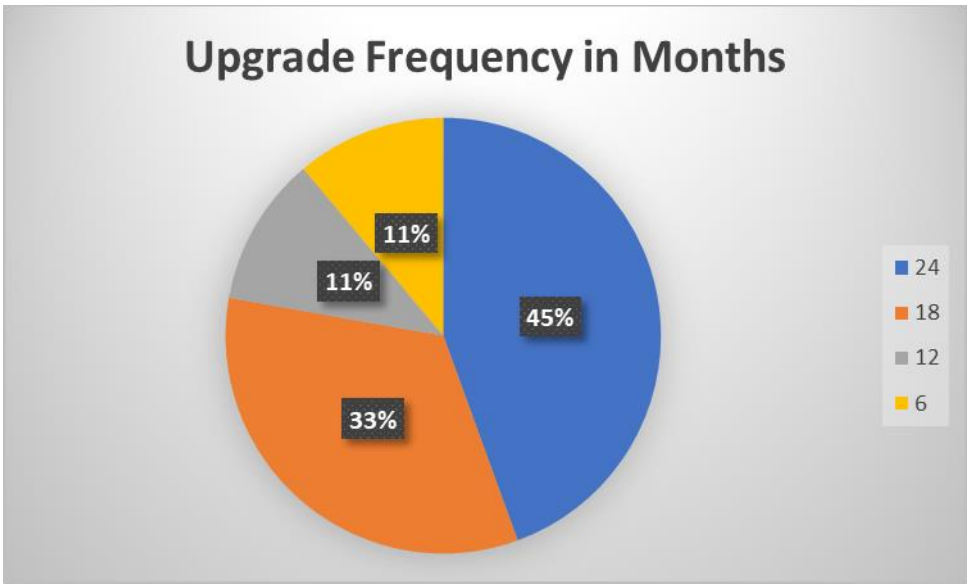


Figure 17 Frequency of line upgrade work

Companies # 1, #6 and #9 reported that line upgrade work resulted in additional evening and weekend shifts, creating additional cost to the business. 55% of the companies surveyed reported that upgrade work takes approximately two weeks. Most of this time is taken up with qualification, validation and change control processes. The addition of aggregation functionality is a major upgrade program. Company #1 reported that an aggregation project would mean a line becoming unavailable for production for between 3 and 6 months.

9.3 Serialisation and productivity

Four companies in the survey were able to identify a cost per pack associated with serialisation. Cost to serialise a pack ranged from 2.5 cents to 6 cents. The average cost was 4.1 cents. This cost aligns with the 5 cent per pack outlined in the 2008 European Commission report (COMMISSION OF THE EUROPEAN COMMUNITIES, 2008b). The Commission report uses a cost of 2 cent per pack after 5 years presumably because of depreciation.

Based on the volumes of production provided in the survey and interview the companies which identified their cost per pack to serialise would have the following annual costs:

Company	Cost per pack	Est. annual units	Cost
Company # 3	2.5c	5m	€125K
Company # 5	6c	60m	€3.6m
Company # 7	5c	90m	€4.5m
Company # 11	3c	50m	€1.5m

Table 4 Serialisation cost per pack

The scale of cost experienced by high volume manufacturers can be seen in Table 3.

Participants were asked if the additional costs associated with serialisation were reflected in the cost of goods or unit cost per item produced. Four of the companies surveyed were able to provide a percentage impact on unit costs.

Company	% increase in COGS/Unit Cost
Company #10	1.9%
Company #5	0.5%
Company #3	2.5%
Company #7	5.4%

Table 5 Impact on cost of goods/unit cost

The average increase in cost of goods reported was 2.6%. In the case of company #7 and company #10 the increase in cost of goods is conservative. The figure was calculated using the depreciation cost associated with serialisation equipment only. It does not consider the labour costs associated with running a serialisation line. The use of depreciation cost is particularly useful when examining the impact of serialisation. Four of the companies

surveyed still consider serialisation process to be in the project phase. Even though serialised lines are in operation, ongoing upgrade work means that project resources are still applied. The costs associated with serialisation can be difficult to calculate as budgets are still split between capital projects, operations, local and corporate company structures. Depreciation however cuts across both capital and operational budgets. By using depreciation costs the researcher was able to calculate a serialisation depreciation factor for productivity calculations. The serialisation depreciation factor SD_f is calculated as:

$$SD_f = \frac{Annual\ Depreciation\ cost}{Unit\ cost\ x\ units\ produced\ per\ annum}$$

The serialisation depreciation factor provides a simple method to capture part of the costs of serialisation as projects move from initial installation through to business as usual (BAU). Survey participants were shown the prediction from the 2008 European Commission report that suggested that the cost of serialisation per pack line at €150,000 per line. Respondents indicated that the cost to serialise a pack line ranged from €250,000 to €900,000 depending on the functionality required. The average cost to serialise a pack line was estimated at €600,000, which four-fold what the E.C. impact report suggested.

These high capital costs have a direct impact on the future operations of the pharmaceutical sites. The capital outlay on serialisation equipment creates a depreciation weight on operational budgets. One participant described serialisation as having no benefit to the business and created a cost that was difficult to pass on to contracted customers. Another respondent described how the weight of depreciation on the budget was restricting the site's ability to invest in other equipment and that the company was unable to pass on the additional costs to their corporation.

Participants were also asked about the ongoing operational costs associated with serialisation. Additional operational costs might include labour costs, data costs, regulatory registration costs and code costs for markets such as China and Russia. While 91% of the companies surveyed cited that serialisation did require additional labour costs, only 55% were able to calculate what the additional labour cost was for their organization. The 2014 Pew

Healthcare report predicted an additional labour costs to manufacturers of €242,000 per annum. Respondents averaged the additional cost of labour at €88,000 per pack line.

Accepting a conservative calculation of an average increase in the cost of goods of 2.7% we can assess the impact across the Irish pharmaceutical market. The Central Statistics office (CSO) in Ireland reported that in 2019 Ireland exported €15.9bn of packaged pharmaceutical goods (Commodity Number 3004). Some of these packaged pharmaceuticals will be filled into their primary packaging containers for export to packing sites outside of Ireland. The CSO does not distinguish between pharmaceutical is primary packaging or fully finished secondary packaged good. If we calculate that one third of exports are in their secondary packaging format and that COGs makes up 25% of sale price (Gyurjyan *et al.*, 2017) then a 2.7% increase in the unit cost is valued at €36m per annum. If intra-company pricing is used for the calculation, then the annual cost is expected to be €143m per annum.

All the companies surveyed, except for one had an in-house lean manufacturing or operational excellence team. When asked if operational excellence programs had pushed their companies to produce more just-in-time orders, to reduce batch sizes and decrease inventory positions, 55% of respondents said that they now processed more batches annually. However, during interviews with participants it was clear that many companies were trying to move away from the pure Just in Time (JIT) approach. Nine of the eleven companies (81%) reported that they were actively increasing batch sizes to achieve productivity gains. The philosophy behind smaller batch sizes comes from both the internal demands of operational excellence programs to minimise inventories and from market driven demand. One participant described how sales and marketing team members needed to understand that pack line machines were built for high volume production rather than small batch runs.

When asked if serialisation had exacerbated the inefficiencies associated with small batches only 55% of respondents agreed. However, among large volume manufacturers 90% of respondents agreed that serialisation processes had put extra strain on changeover times and efficiencies. Company #10 described a batch that might take 10 minutes to run but one hour to setup. Three companies described how they had decoupled upstream filling from the pack lines to allow the pack lines to produce high volume batches more effectively.

10. Conclusions

The aim of this research was to determine the impact of serialisation on operational efficiency and productivity on Irish pharmaceutical sites. The research had three objectives, firstly to to test the assumptions made by industry bodies and policy makes in advance of the implementation of serialisation. Secondly, to assess the impact of serialisation on operational efficiency and finally to determine the impact of serialisation on site productivity,

The research found that serialisation did have a negative impact on operational efficiency in Irish pharmaceutical sites. There was some postulation in the literature prior to the implementation of the Drug Supply Chain Security Act (DSCSA) and the European Falsified Medicines Directive (FMD) that serialisation could provide improvements in operational efficiency. There was an argument that new equipment and interconnected systems could improve operational effectiveness. These efficiency improvements have not manifested themselves in the Irish context.

Operational Equipment Effectiveness (OEE) is a key measurement of efficiency. The research found that post serialisation efficiencies have dropped on the Irish manufacturing sites surveyed in this research by an average of 2.71%. Adjusting for two companies that reported zero negative impact on OEE despite having reported additional time required for batch changeovers, the research revealed a 3.8% loss in OEE.

The research points to a limited implementation of OEE systems in Irish pharmaceutical manufacturing sites. While 89% of the sites surveyed gathered OEE data it seemed there was a lack of benchmarking of OEE data prior to serialisation. Many sites only recorded data on a limited number of pack machines. Some sites pointed to delays in machine setup due to serialisation but also reported a zero loss of OEE.

Line availability is an important component of OEE calculations. Continuing changes to regulations and the adoption of serialisation in new markets mean that that pack lines are often removed from production duties for upgrade work. This loss of availability is not captured in the OEE calculation as the machine loss is recorded as planned downtime. 55% of survey participants recorded carrying out upgrade work every 18 months or less. Typical downtime was 2 weeks. Major upgrade work such as the addition of aggregation functionality

might mean the loss of a line for between three and six months. The loss of availability from these lines targeted for upgrade means additional labour costs for the business. Other production lines need to work longer hours to take up the slack. Only one third (36%) of the companies surveyed used measurements to capture this significant loss of line availability.

Because of the ongoing upgrades to serialisation equipment there is an overlap between capital projects and operations in Irish pharmaceutical sites. It is difficult to track the costs associated between capital projects and operations. The Serialisation depreciation factor **SD**f provides a simple calculation to assess the impact of serialisation on unit cost. Capital costs accrued in the project phase of serialisation are reflected in operational costs through depreciation line items.

The impact of serialisation on unit cost and cost of goods is not insignificant. Using the **SD**f calculation the researcher could calculate the impact of serialisation on unit cost as an increase of 2.7%. Based on Irish Central Statistics office figures this represents an increase in the cost of packaged pharmaceutical goods exported from Ireland of between €36m - €143m per annum (depending on whether distribution or intra-company pricing is used) Some participants in the survey complained that their businesses were expected to absorb these additional costs. Research would indicate that these additional costs are ultimately passed onto patients and payer organizations (Suresh and Basu, 2008). Some companies had calculated a cost per pack for serialisation. The average cost per pack was 4.1 cents. For large volume sites the annual cost of serialisation is significant running to millions of euro per annum.

The research also identified a trend in Irish based pharmaceutical sites away from just-in-time manufacturing. 81% of participating companies reported that they were actively seeking to increase batch sizes and decrease their product range to claw back operational efficiency. While no correlation could be made that serialisation exacerbated the impact of smaller batches on pack line efficiency it was clear that the companies surveyed were intent to increase batch sizes to achieve better efficiency.

The research also looked back on the assessments of policy makers and industry bodies in advance of the track and trace regulations. From the literature it was clear that little if any consideration was given to the potential impact of serialisation on efficiency and productivity.

Estimations by policy makers on the cost on the costs associated with serialisation were also inadequate. This research indicated that policy makers underestimated the cost of serialisation projects by a factor of four. A 2008 European Commission Assessment report had predicted an average cost of serialisation per pack of 5 cents. This figure aligned with the experience of the survey participants which reports a 4.1 cents average cost per pack for serialisation. The average cost per pack is a telling indicator. High volume sites report an annual cost of serialisation of up to €4.5m per annum.

The 2018 ISPE report used in the survey was found to be reliable in terms of the experiences of the sites interviewed. The overall result postulated in the report aligned with the experience of participants in the year after serialisation implementation. However, the impact on efficiency immediately after the implementation of serialisation was much more acute in the Irish context.

As a follow up to this study further research could be conducted to narrow down the annual cost of serialisation in Irish pharmaceutical sites. This study might require access to financial managers to get access to data on depreciation and operational costs. A study on the fundamental question of the effectiveness of the falsified medicines directive might also be worthwhile. Did all the effort to serialise medicines meet its objective to protect drug supply chains, particularly in developing countries? Finally, a study on the impact of Brexit on serialisation processes might prove to be insightful.

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12. Appendix

12.1 Survey

The impact of serialisation on operational efficiency and productivity in Irish pharmaceutical sites

Dan O Mahony Masters Thesis - August 2020

The confidentiality of this questionnaire is imperative.

Every effort is taken to maintain the anonymity of the respondent and the anonymity of the company for which they work. Participants in this survey will not be asked for their names or the names of their company. While participants will not be asked for specific information that might identify themselves or their company.

A method of pseudonymity is used to protect the identity of the participants and their employers. Pseudonyms are used in the preparation of written transcripts from the respondents and in any subsequent documents or publications. Pseudonyms will be adopted as soon as possible within the transcription and analysis phase. Each participant will be assigned a code. The register of codes and names will be held on a written sheet, stored in a locked cabinet. Video recordings made during the interview process will be immediately deleted following transcription and anonymisation. Any printed copies of the transcription will be held in a locked filing cabinet. Soft copies of the transcribed interview will be stored electronically using encryption and password protection.

Participant Code

Department

Years of service in the pharmaceutical Industry

Company Profile

- ☐ OSD Blister pack
- ☐ OSD Bottle
- ☐ Vials
- ☐ Ampoule
- ☐ Prefilled Syringe
- ☐ Inhalers

Number of Pack Lines

Age of Pack Lines

Number of serialised Lines

Number of aggregated lines

% of Lines retrofitted for serialisation

When did the serialisation project start?

In advance of serialisation implementation the European Commission published an impact assessment report that estimated the cost of serialisation per pack line at €150,000.

What cost would you assign to serialise a pack line?

Did serialisation lead to an increased labour costs directly and indirectly?

Number of additional staff associated with serialisation

Number of packs produced per year

Number of staff involved mostly on serialisation

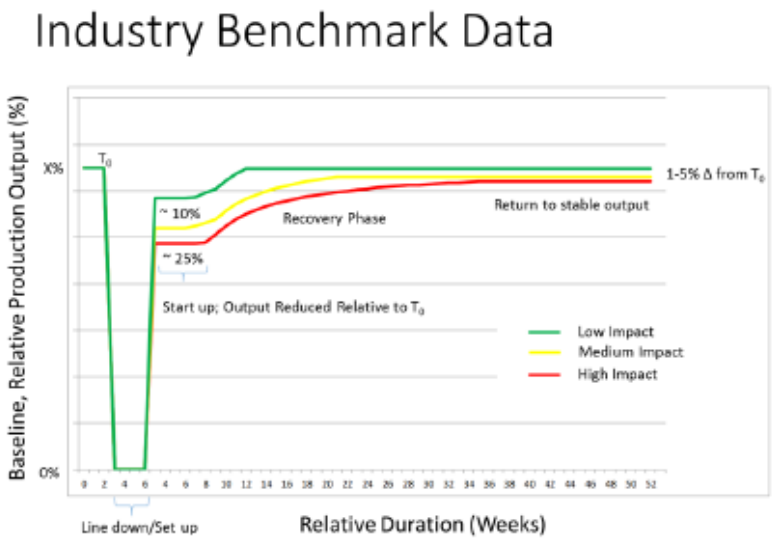
Is pack-line OEE measured?

How is OEE Measured?

If automated, what system is used?

3

A 2018 article published in the ISPE magazine, estimated that serialisation would cause an OEE loss of beween 10% and 25% in the period immediately after implementation. After 6 months the OEE situation would recover to between a 1 - 5% loss. What was the experience in your company?



Did the serialisation process impact pack-line OEE post implementation?

% Impact on OEE up to 3 months post serialisation?

% Impact on OEE between 3 and 6 months post serialisation?

% Impact on OEE between 6 and 12 months post serialisation?

% Impact on OEE after 12 months post serialisation?

How was OEE recovered or other comments on OEE post serialisation ?

e.g. better use of serialisation equipment/compensatory measures (measures not related to serialisation)

A European Commission Impact Assessment report predicted that serialiation would cost 2c per pack during the first 5 years post implementation, falling to 0.5 cent per pack after 5 year.

Does that prediction sound right?

Has the business estimated the cost per pack for serialiation?

If YES, what is the cost per pack in € cent?

A Pew Healthcare report in 2014 refernced the additional labour cost to run a packline post serialisation at $291,000 (€242,000) per annum. Taking into account the partiscipation of IT, serialisation SMEs, artwork, project management does that cost sound right?

Would you agree with this estimate?

Could you put an estimate on the additional labour costs per anum due to serialisation?

Nakajima in the seminal work, Total Productive Maintenance (TPM) identified six factors that had the most impact on OEE. These are known as the big losses.

(i) Equipment failure/breakdown losses

(ii) Setup/adjustment time

(iii) Idling and minor stop losses

(iv) Reduced line speed

(v) Reduced yield until machines stabilise

(vi) Quality

Does serialisation Print + Check processes cause equipment failure i.e. poor print

If so how?

Do setup times take longer because of serialisation? If so how?

Examples: challenge runs, getting serialisation data, clearing data, reconciling serial codes

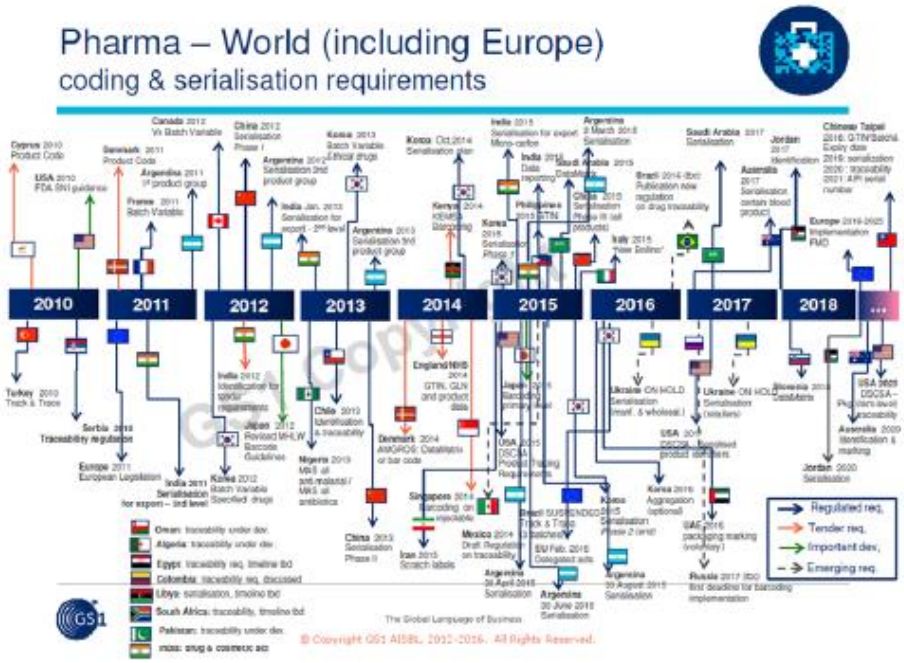
Do lines run at rated speeds? If not, is this partly to ensure that serialisation print and check does not fail?

Examples: challenge runs, getting serialisation data, clearing data, reconciling serial codes

Quality. Are there reworks because of serialisation processes?

Examples: challenge runs, getting serialisation data, clearing data, reconciling serial codes

Since the initial implementation of serialisation there has been a regular need to meet new regulatory requirements in different markets. How have these new requirements impacted pack line availabilty?



How often in months do lines need to be taken offline for updates and patches?

If lines are made unavailable for serialisation patches and upgrades is this recorded as planned downtime or maintenance?

- ◯ YES
- ◯ NO

Can you describe the impact of patches and upgrades on line availability and OEE?

Another efficiency measurement, OEEM is similiar to OEE except that it takes into account planned downtime. OEEM multiples OEE by an availability factor Apm. OEEM accounts for the loss of availability due to planned maintenance.

Does your company measure OEEM?

Another alternative measure to OEE is the Equipment Effectiveness rate (E_R). The equipment effectiveness E rate has three factors similar to OEE; Yield Y, Rate R and Availability A. The Availabilty Factor is calculated A_R by taking into account the impact of planned and unplanned downtime. It is calculated as follows:

$$A_R \text{ Availability Rate} = \frac{\text{(Productive Time + Planned Downtime + Unplanned Downtime)}}{\text{Productive Time}}$$

Does the company use the Equipment Efficiency factor to account for line availability?

Would the Equipment Efficiency factor be a useful measure for the business?

Are the Cost of Goods (COGs) discussed at an operational level?

If serialisation processes require additional resources in terms of hardware, software and labour have these costs been reflected in the Cost of Goods at the company?

If serialisation has impacted the cost of goods, could you estimate the % change in cost of goods?

Many pharmaceutical companies started operational excellence programs in the mid 2000s. The drive toward operational excellence has driven companies to reduce inventories. This has led to "make to order batches".

Does your company have an operational excellence or lean manufacturing program?

- ☐ Operational Excellence
- ☐ Lean Manufacturing program
- ☐ Other
- ☐ No continuous improvement program

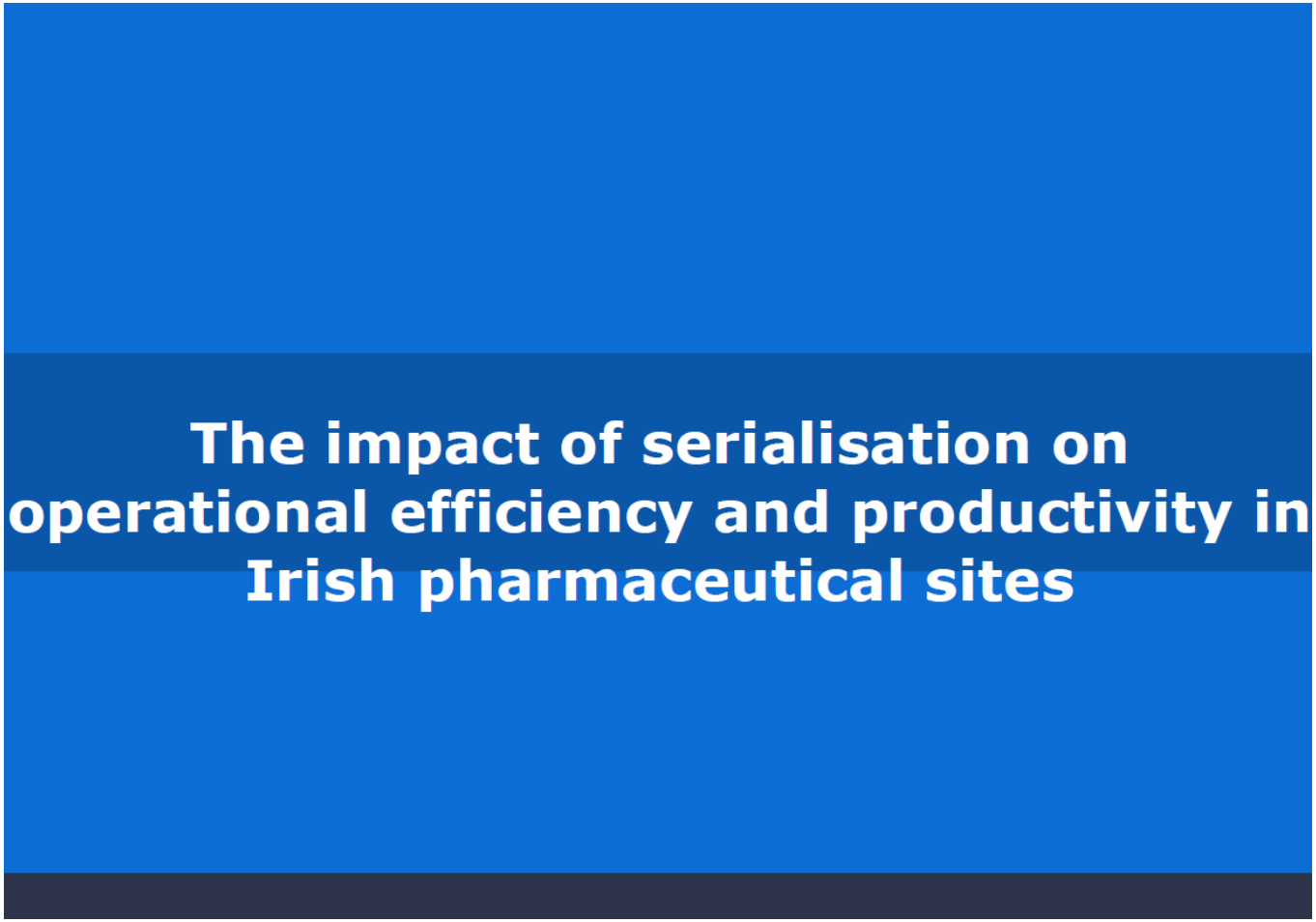
Have you seen an increase in the number of batches processed per month over the last five years?

Can you provide some detail on the changes in batch size and the number of batches processed?

If the number of batches has increased, has this impacted on OEE?

If the number of batches has increased, then has this exacerbated the impact of serialisation processes on OEE?

12.2 Consolidated Report from survey and interviews



The impact of serialisation on operational efficiency and

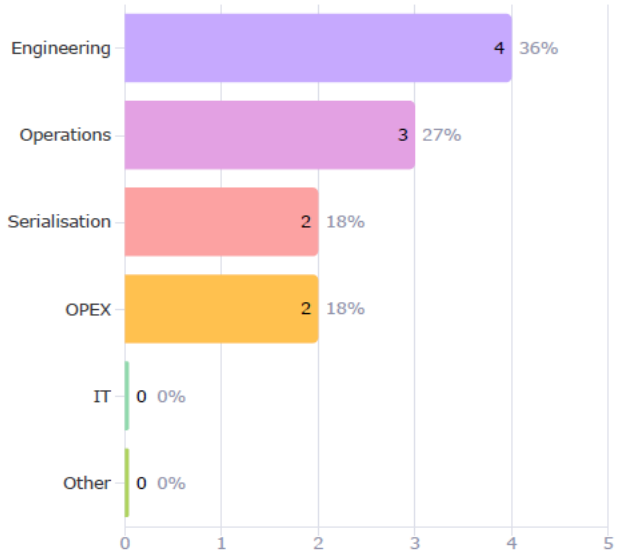
Participant Code

11 Responses

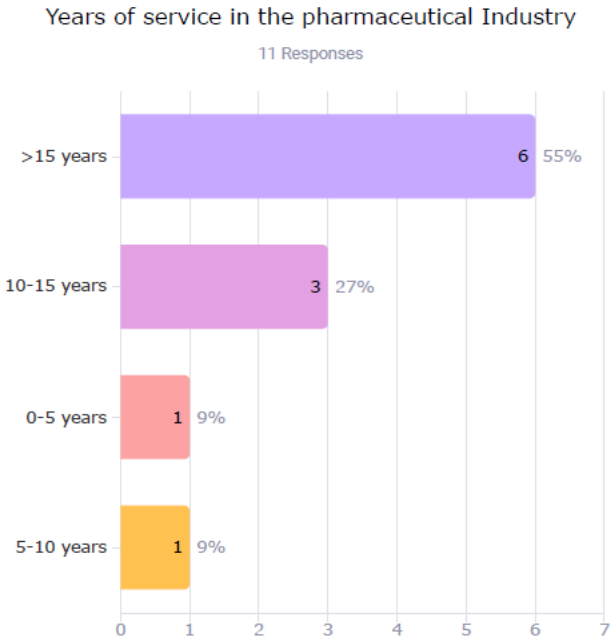
Data	Responses
013	1
012	1
011	1
009	1
010	1
008	1
006	1
007	1
005	1

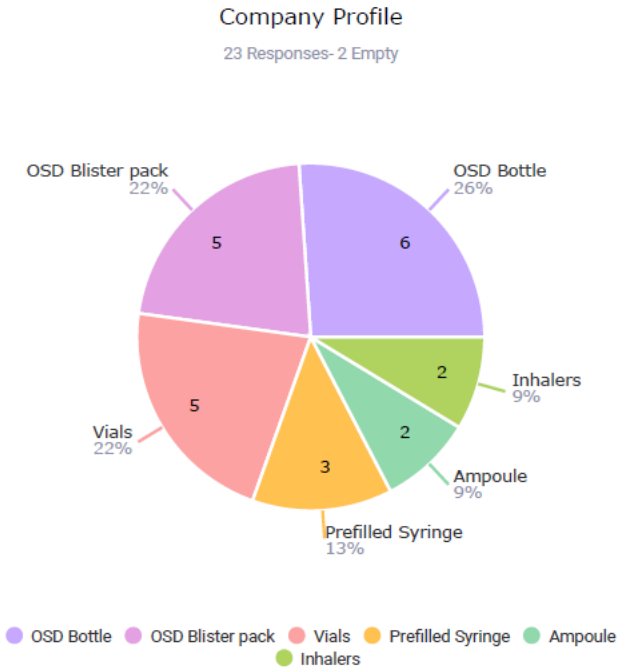
Department

11 Responses



The impact of serialisation on operational efficiency and





The impact of serialisation on operational efficiency and

Number of Pack Lines

11 Responses

Data	Responses
8	3
7	2
15	2
13	1
11	1
3	1
10	1

Age of Pack Lines

11 Responses

Data	Responses
8 on average	1
topical medicines	1
10	1
18	1
less than 5 years	1
Average 8	1
New to 15 years	1
12 on average	1
2011 2012	1

The impact of serialisation on operational efficiency and

% of Lines retrofitted for serialisation

11 Responses

Data	Responses
100	4
90	2
70	1
85	1
50	1
60	1
0	1

When did the serialisation project start?

11 Responses

Data	Responses
2012	3
2015	2
2017	1
2014	1
2016	1
2011	1
2013	1
2018	1

The impact of serialisation on operational efficiency and

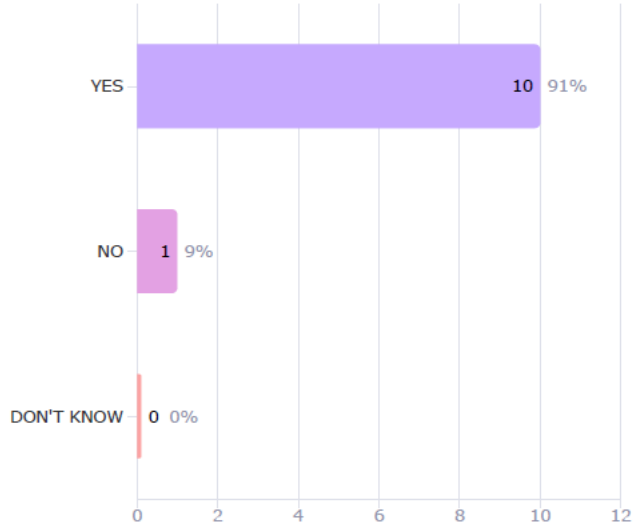
What cost would you assign to serialise a pack line?

7 Responses- 1 Empty

Data	Responses
250000	1
600000	1
500000	1
$1m	1
700000	1
800000	1
450000	1

Did serialisation lead to an increased labour costs directly and indirectly?

11 Responses



The impact of serialisation on operational efficiency and

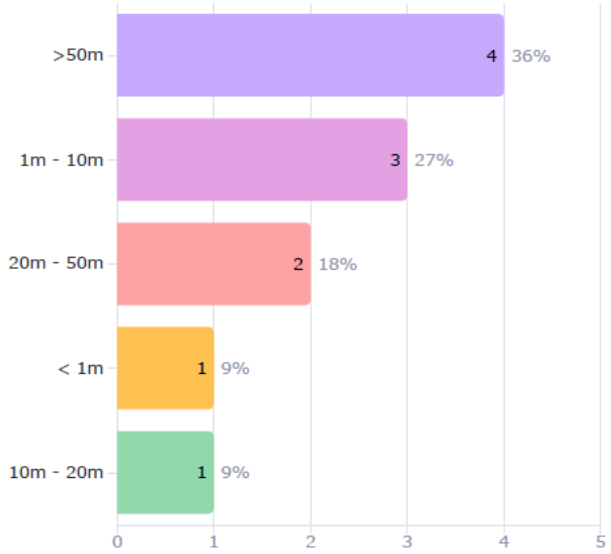
Number of additional staff associated with serialisation

10 Responses

Data	Responses
5	2
10	2
0	1
50	1
100	1
30	1
13	1
0.5	1

Number of packs produced per year

11 Responses



The impact of serialisation on operational efficiency and

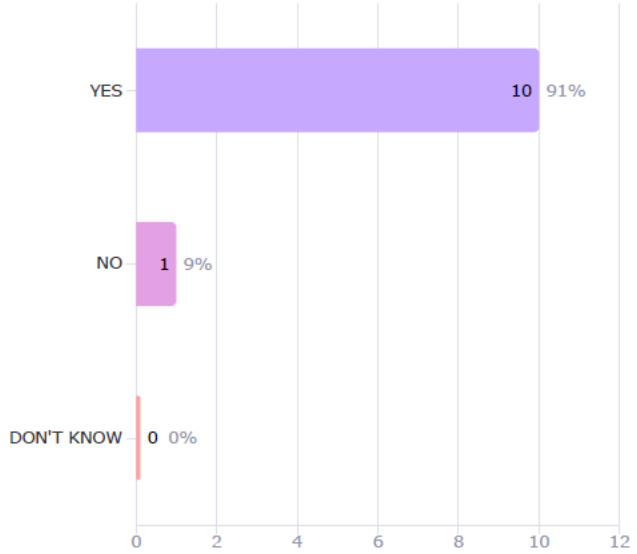
Number of staff involved mostly on serialisation

10 Responses- 1 Empty

Data	Responses
3	3
1	2
9	1
2	1
.25	1
500	1
12	1

Is pack-line OEE measured?

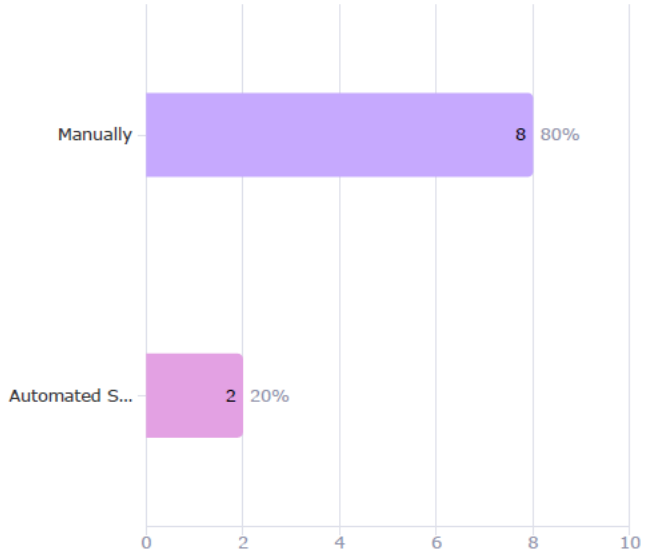
11 Responses



The impact of serialisation on operational efficiency and

How is OEE Measured?

10 Responses- 1 Empty



If automated, what system is used?

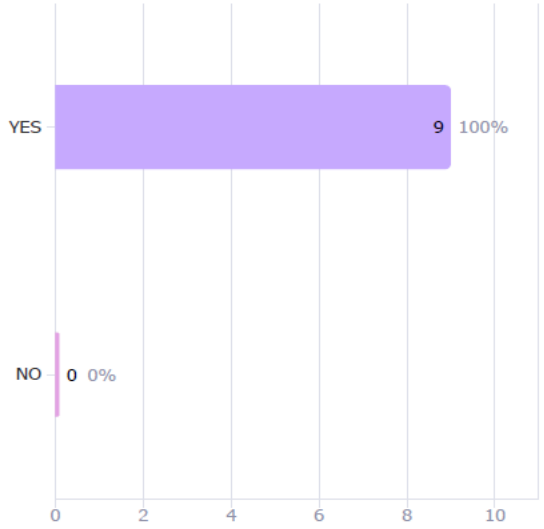
9 Responses- 2 Empty

Data	Responses
Antares + Crest support	1
Manual input into automated system. Bespoke corp solution.	1
Machine level on one machine	1
OSI PI planned	1
Plan to automate over next period. OSI PI	1
Providum with manual reporting	1
Some automated systems in development	1
MDPI Bespoke + PLC system	1
PIMS Werum	1

The impact of serialisation on operational efficiency and

Did the serialisation process impact pack-line OEE post implementation?

9 Responses- 1 Empty



% Impact on OEE up to 3 months post serialisation?

8 Responses- 1 Empty

Data	Responses
30	2
15	2
20	1
11	1
50	1
5	1

The impact of serialisation on operational efficiency and

% Impact on OEE between 3 and 6 months post serialisation?

7 Responses- 2 Empty

Data	Responses
5	2
30	1
6	1
25	1
3	1
15	1

% Impact on OEE between 6 and 12 months post serialisation?

7 Responses- 2 Empty

Data	Responses
20	1
8	1
5	1
10	1
2	1
0	1
12	1

The impact of serialisation on operational efficiency and

% Impact on OEE between 3 and 6 months post serialisation?

7 Responses- 2 Empty

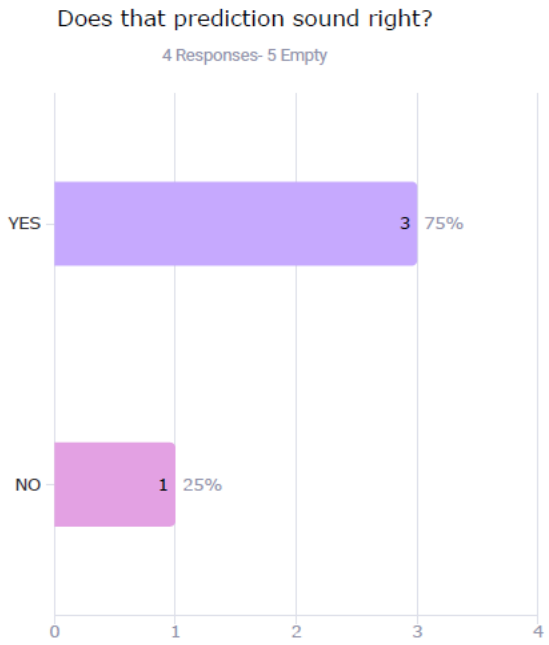
Data	Responses
5	2
30	1
6	1
25	1
3	1
15	1

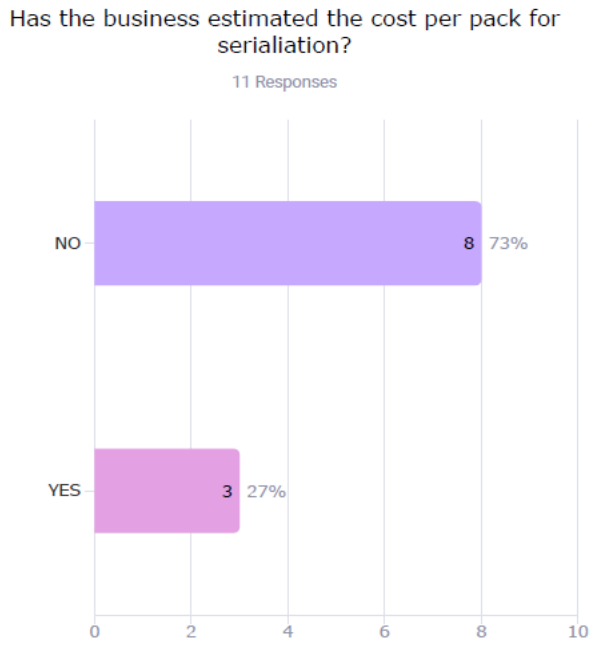
% Impact on OEE between 6 and 12 months post serialisation?

7 Responses- 2 Empty

Data	Responses
20	1
8	1
5	1
10	1
2	1
0	1
12	1

The impact of serialisation on operational efficiency and





The impact of serialisation on operational efficiency and

If YES, what is the cost per pack in € cent?

3 Responses- 6 Empty

Data	Responses
0.03	1
0.5	1
.06	1

Could you put an estimate on the additional labour costs per anum due to serialisation?

9 Responses- 1 Empty

Data	Responses
Not really. There are capital costs.	1
Global and local resources. €88K	1
No	1
High value, lower volume not as critical a meassurre	1
€75K per line. 3 Heads added. Serialisation was allowed in budget.	1
€35K including project	1
Minutes lost due to OEE. $165K	1
3 Antares Support people, BPO additional costs . per line €25KEMVO/NMVO fees.	1
Not really. Could argue for 60K but that has not been	

The impact of serialisation on operational efficiency and

Does serialisation Print + Check processes cause equipment failure i.e. poor print

11 Responses

Data	Responses
Print quality and character recognition. Readability with cameras. Character recognition. Took out characters	1
There are still daily print failures. that cause rework. After sampling go back to last good point. IPC. 30 mins. 6000 units visually inspected or reworked. Customer complaints on scanning. Incorrect character details for particular markets. Chinese market legibility.	1
No so much any more. Runs reasonably smoothly.	1
Plenty issue on start up phase. Regular enough	1
Negligible	1
Negligible. Not common.	1
Low to negligible. Laser and inkjets (less reliable) blocked nozzles on inkjet dust build up on lasers	1
There can be issues but minor at this point. Aesthetics	

Do setup times take longer because of serialisation? If so how?

11 Responses

Data	Responses
Setup time was impacted. Up to one extra hour at the start. Printing on both sides of flaps. 15 - 20 mins per batch. Check data. Quality checks and Challenges.	1
Significant addition to setup time. Number changes. 30 to 45 mins. batch change. 50% increase. Aggregation format change goes from 2.5 hrs to 3 hrs. reconfigure equipment means more challenges	1
It does add some time. reconciliation and paperwork. SCADA + EBR in formulation but not packing	1
Some time loss. Good rejects. De-Serialize rejects. Break down pallets Build up pallets. Not major.	1
Other activities in parallel. Does take time but doesn't slow batch	1
Setup times. Must call in tech for serialisation related downtime. Reconciliation of serialisation batches. Movement of mobile serialisation equipment. Overall changeovers went up to 45 minutes initially. Now down to 20 mins. 11% given over to serialisation processes.	1

The impact of serialisation on operational efficiency and

Do lines run at rated speeds? If not, is this partly to ensure that serialisation print and check does not fail?

10 Responses- 1 Empty

Data	Responses
No	3
Some cases lines run slower because of serialisation. Give printers a chance to print. Print quality. Up to 10 to 15% reduction in speed. Dependednt on particular batches and packaging. Injket and laser. Laser = vibration. Inkjet - material. Gluing, anti tamper. Drying rates. Divets and bumps for laser printing. Materials are a different dept.	1
No. Line speeds are optimised for pack quality. Serialisation itself is capable of high spreed but the material itself may not be able to match.	1
140/170 Bottling line speed issues	1
No impact. Lines have slowed. 5 - 10 % currently.?	1
No issue there	1

Quality. Are there reworks because of serialisation processes?

11 Responses

Data	Responses
early on but now under control	1
Print quality	1
Some reworks. Not common.	1
No	1
Sometimes. delay in getting data uploaded. Does cause a delay in next batch. Every couple of months.	1
No.	1
Limited. maybe 3 - 4 months across all lines. Operator mistake Software misalignment - out of sync. Downtime hours to days	1
negligible	1

The impact of serialisation on operational efficiency and

How often in months do lines need to be taken offline for updates and patches?

11 Responses

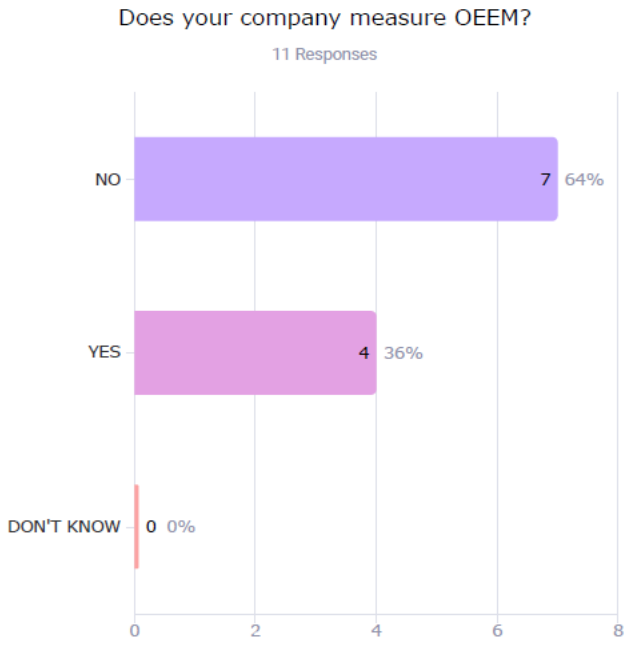
Data	Responses
18	4
12	3
4	1
6	1
0.5	1
24	1

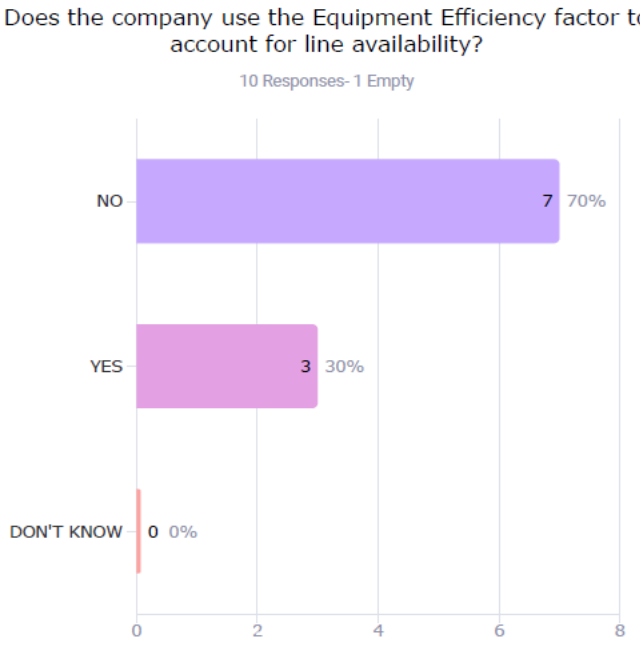
Can you describe the impact of patches and upgrades on line availability and OEE?

11 Responses

Data	Responses
Lines may not need to be re-qualified. Only for reimbursement numbers. Done between batches	1
Goes into planned maintenance. Full week of production downtime. 24/7 run. Lose 5 production days. 120 production hours. 570K unit equivalent. Once per year going to twice per year. Plus every one day every 2 months for trouble shooting and training. Potential site for production is measured.	1
Part of planned maintenance. Weekends and long weekends. Validation and change control. Must go through approval process and change control.	1
Aggregation Russia Saudi Planned downtime. Line setup means lines are dedicated for activity. taking down lines. 4 shifts. Using up labour resources. Continental shifts	1
Software upgrade. 2 weeks. validation? OEEM not used because of plenty of capacity on other lines.	1
Shutdowns 2 x per year. Upgrades can take 10 - 12 days per line. Evening and nights work This is included	

The impact of serialisation on operational efficiency and

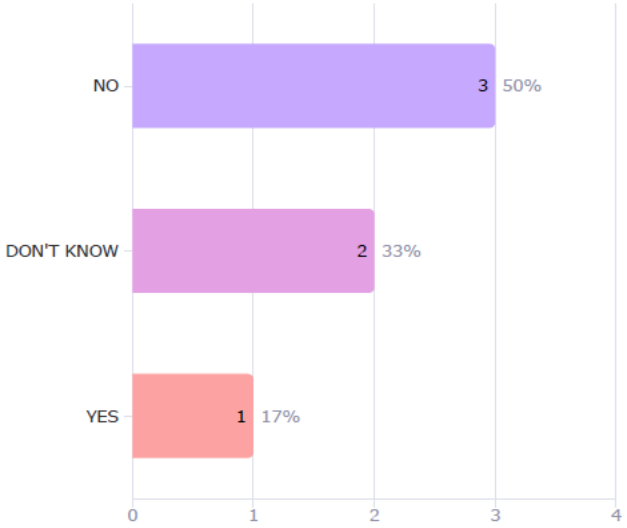




The impact of serialisation on operational efficiency and

Would the Equipment Efficiency factor be a useful measure for the business?

6 Responses- 3 Empty



Are the Cost of Goods (COGs) discussed at an operational level?

11 Responses

Data	Responses
3c in additional cost. Redesign cartons Low impact Pricing structures did not allow cost to be recouped. Business carried the cost Aggregation could help	1
Costs for projects. Unit cost is measured. Serialisation isn't broken out.	1
Sometimes. Discussed as unit cost.	1
Process effectiveness Pe measurement	1
Review on a monthly basis. Upgrade work is taken into account.	1
Yes. targets on Cost of Goods. Unit cost is for site i.e. all activities Packing proportion is large compared to effort. 30% of cost relates to packaging.	1
Yes. Minimize impact.	1
Yes. Reportable measure in KPIs.	1

The impact of serialisation on operational efficiency and

If serialisation processes require additional resources in terms of hardware, software and labour have these costs been reflected in the Cost of Goods at the company?

9 Responses- 2 Empty

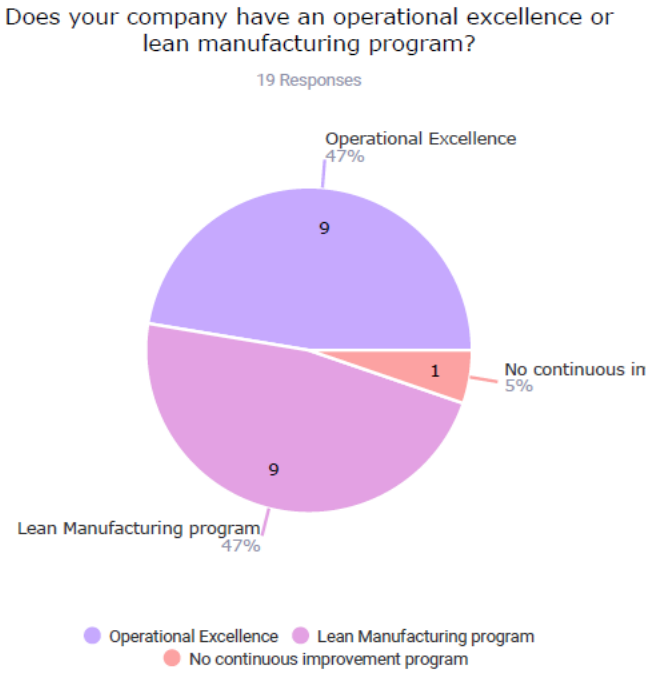
Data	Responses
Maybe 1.9%	1
Costs are at a tipping point now. Volumes are increasing and productivity	1
Serialisation is not discussed in relation to COGS. How does large serialisation spend get accounted for. causes pressure on site to compensate for depreciation loss. Impacts site ability for new capex Standard costs should be adjusted	1
During monthly review. Not calculated as a percentage.	1
Hass added resources and time. 3rd shift will effect productivity and related to more batches and serialisation	1
Yes. Automatic case packers No impact on COGS but certainly less than 1% due to high volumes (and higher margins)	1

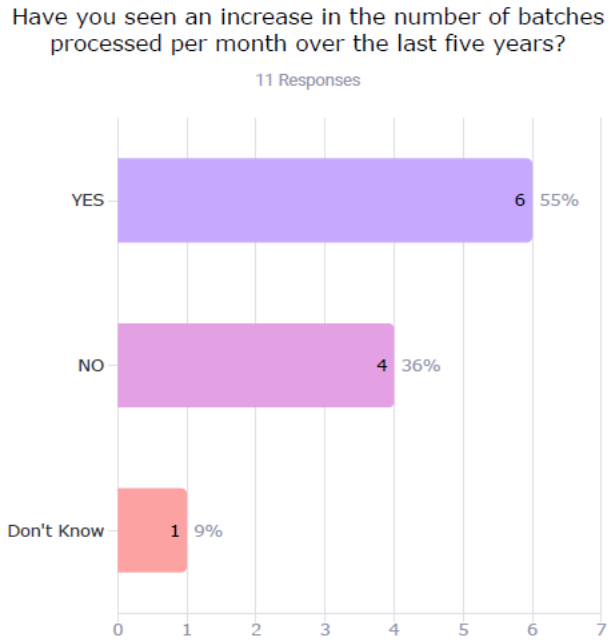
If serialisation has impacted the cost of goods, could you estimate the % change in cost of goods?

4 Responses- 5 Empty

Data	Responses
1.9	1
5	1
0	1
0.5	1

The impact of serialisation on operational efficiency and





The impact of serialisation on operational efficiency and

Can you provide some detail on the changes in batch size and the number of batches processed?

9 Responses- 2 Empty

Data	Responses
reduce cost of drugs. Drive to reduce by 25%. Never turn down an order. Very small batches. 10 mins production= 1 hr setup MOQ - merge markets Introducing MOQs Simplify packaging Different leaflets. Bigger batches now, opposite to before 20% reduction in cost	1
Batch sizes went up More batches also went up Hence more machines	1
Made frequency targets Changeover more regular Customer obsession? Do sales understand that machines are built for volume production	1
Batch numbers have increased 100% increase in volume Batch sizes are coming down New markets Maximising shelf life Driven by lean inhouse	1
580 batches 2018 1200 - 2019 Doubled batches for 5% increase in volume	1
Decoupling filling lines and packing lines. Brightstock with late stage customisation. Bigger impact on fill lines. Demand may be higher than supply so difficult	1

If the number of batches has increased, has this impacted on OEE?

8 Responses- 3 Empty

Data	Responses
No	2
Small batches also increased. Market driven demand We produce for stock as a necessary medicine/life saving Essential medicines.	1
Negative impact	1
Yes. Significant.	1
YES! 5000 on average now some are less than 100. OEE 6% to 55%.	1
No. Not distinguished.	1
Yes. Move away a little from JIT to do greater batch runs.	1

The impact of serialisation on operational efficiency and

If the number of batches has increased, then has this exacerbated the impact of serialisation processes on OEE?

10 Responses- 1 Empty

Data	Responses
No	4
we are increasing batch sizes. Less changeovers with serialization. Split batches afterwards.	1
greater	1
The two impacts do coincide. Lines not designed for changeover. Two trends coming together.	1
Yes. Multiple times.	1
20 mins	1
Yes	1

Thank You!

The impact of serialisation on operational efficiency and productivity in Irish pharmaceutical sites