Lean Thinking for Regulatory Processes

By Aisling Foley

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Declaration

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Declaration:

"I hereby declare that this project is entirely my own work and that it has not been submitted for any other academic award, or part thereof, at this or any other education establishment".

Aisling Foley

Abstract

Medical Device Manufacturers are faced with the challenge of changing regulations. Although there are global harmonization efforts, regulations are become more complex and challenging to manage. In the next few years' manufacturers must manage significant transformations to their organization due to the changes in regulations e.g. EU MDR and MDSAP. Not all manufacturers are able to allocate sufficient resources to handle the changes. Instead of adding more resources, manufacturers should look at smarter ways manage their regulatory processes. While some companies are taking innovative steps to changing the way they manage regulatory compliance, it is not something that is widely adopted in industry. There is hesitation to change the way we work for fear of cost implications, project delay and even product withdrawals. In Regulatory Affairs, the instinct may be to provide too much information, to cover all potential scenarios. However, provided the risk to the patient is always at the forefront, over-information may be to our detriment. Over-information is a form of waste, as it hides problems and inefficiencies. There are many forms of waste in Regulatory processes e.g. over-information, rework, waiting. If manufacturers look at smarter ways to manage the processes, they can reduce the waste, reduce the process time, improve compliance and improve quality of data. Lean tools are an excellent way to manage these process transformations. Using lean tools like Kaizen, Just-in-Time, Kanban, Standardisation and 5S manufacturer can transform these processes. Although there are challenges with using lean tools, the challenges can be overcome through education and training of employees; commitment from management to drive the lean culture; and through the correct use of lean tools. The medical devices industry is an innovative and competitive industry. For manufacturers to stay competitive they must be able to bring their products to market in quick and cost effective way. The manufacturer that uses lean tools on their regulatory processes, will be able to get their products to market quicker than those who don't use lean. Not only does the use of lean tools benefit the manufacturer, it ultimately benefits the patient, as new products will be brought to the market quicker than before.

Acknowledgements

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1 Chapter 1: Introduction

The Medical Device industry has seen rapid growth over the past number of years, in 2015 the global medical device market was valued at $228 billion, up from $164 billion in 2010. With an expected compound annual growth rate of 4.4%, the market is estimated to grow to a phenomenal $440 billion by 2018 (Cunningham *et al.* 2015). There are many contributing factors to this rapid growth, including the growing aging population which will place an increased demand on medical devices. A report published by the Department of Economic and Social Affairs Population Division has projected that the worlds percentage population aged 60 or over will grow by 56%, from 901 million to 1.4 billion between 2015 and 2013, and by 2050 it will double to nearly 2.1 billion (*World Population Ageing 2015* 2015). Advances in emerging markets such as Russia, China, Brazil and India are expected to have a significant influence on the medical device industry of the next fifty years (Cunningham *et al.* 2015). As there is increasing demand on the international medical device market, there comes an increasing demand on regulations.

The last few years have seen significant regulatory changes in established markets and in emerging markets. 2017 has seen introduction of the new European Medical Device Regulations ('REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL' 2017) and India has introduced new Medical Device Rules for a more formalized registration process (*Health Ministry Notifies Medical Devices Rules, 2017* 2017) The Malaysian Medical Device Authority (MDA) are in the process of overhauling their regulatory system (Eisenhart 2017). In 2014 Japan replace the Pharmaceutical Affairs Law (PAL), making the Pharmaceutical and Medical Device Law (PMD Law) the main medical device regulation (*Pharmaceutical and Medical Device Agency* 2017). Also in 2014, the EEU (The Eurasian Economic Union) was established as part of a treaty signed by Belarus, Kazakhstan, Russia, Armenia and Kyrgyzstan. As part of this treaty the Eurasian Economic Commission (EEC) was established as the permanent regulatory body of the EEU, which will allow manufacturers to streamline their product registrations in all five member states (*AGREEMENT On the Uniform Principles and Rules Governing Market Circulation of Medical Devices within the Eurasian Economic Union* 2014). This is only a sample of the global regulatory changes. A lot of these updates have been framed in conformity with global regulatory harmonization efforts but despite harmonization efforts regulatory compliance is becoming increasingly complex for manufacturers. In a survey completed by the Emergo Group on over 3,000 medical device industry participants, one of the key findings was that regulatory changes continue to represent the biggest business challenge. It is perceived that markets such as Brazil, Japan, Mexico and in particular, Europe, will be more difficult to obtain regulatory approval in 2017 (Emergo 2017). These regulatory changes are going put a significant strain on resources. The changes to regulations are out of the control of manufacturers but the manufacturer can control how they manage them. Manufacturers need to work more efficiently and effectively if they are going to manage this increasing workload.

Regulations are increasing in complexity. This is adding an increased demand on resources to manage regulatory compliance. While global harmonisation efforts are on-going, efforts like

this take time e.g. it took the European Commission five years to agree on the new regulatory framework for medical devices and in-vitro diagnostics sold in Europe. Instead of waiting for improvements to global regulatory harmonization, the manufacturer needs to look at how they work and how they manage all the different regulatory functions and associated roles. Manufacturers are going to need more resources to manage these increasing regulatory requirements. Unfortunately, not all companies can afford to take on a lot of new resources, or they may not be able to find the appropriately qualified people. If a manufacturer is unable to maintain compliance to regulations, they face the prospect of having products withdrawn from the market. Instead of pumping more resources into regulatory compliance, manufacturers could look at changing how they work. They need to be smarter and more innovative in how to manage their regulatory processes. There are many ways a manufacturer can improve how they work. One concept that was used effectively in manufacturing since 1940's is Lean Manufacturing.

Even though lean concepts have been in practice for over 70 years, the term "lean" was coined by Womack *et al* in 1991 (Womack *et al.* 1991). A common definition of lean, is to produce higher quality products or services, at lower costs and reduced lead times, through the elimination of waste (Cherrafi *et al.* 2016). There are many quantitative and qualitative benefits to implementing lean processes. The quantitative benefits include reduced lead times for the process, reduced inventory, reduced scrap and defects in the process, improved quality of product/service, and reduced costs. The qualitative benefits include improved company morale, more effective communication, enhanced decision making skills, better root cause analysis and improved job satisfaction (Bhamu and Singh Sangwan 2014). Lean looks at reducing waste in the process without requiring additional resources. There is a lot of data outlining the benefits of using lean tools in manufacturing. Lean is commonly used to improve a manufacturing process but it can also be used to optimise business processes (Thompson 2005).

Lean principles are not new to the medical device industry but its use may be more focused on the production lines where "waste" is more visible. Regardless of if it is a production line or a business process, there is always waste in the process, including regulatory process. The seven types of waste that can be found in a process are transport, inventory, motion, waiting, over-processing, overproduction/ over-information, and defects (Womack and Jones 2003). A process is defined as "a series of actions or steps taken in order to achieve a particular end" (Stevenson 2010)**.** Any task in a regulatory role that has a series of actions that need to be followed to achieve a particular goal, can be described as a regulatory process. Examples of regulatory processes can include but are not limited change control, complaints evaluation, medical device reporting and technical file generation. Examples of waste within these processes could be document rejections, requests for further information, unnecessary emails, and over-information. There are many different tools to use in lean, many of which can be applied to regulatory processes e.g. *kaizen* which translates as "continuous incremental improvement" (Womack and Jones 2003). *Kaizen* is ideal for improving regulatory processes, as it looks at how to eliminate waste and non-value added items from the process, without changing the process, and therefore without affecting compliance.

Lean is widely accepted in many industries regardless of the product or service (Jasti and Kodali 2015). There is a wealth of data on lean manufacturing and the impact it can have on processes. The medical device industry is faced with the challenge of dealing with complex regulations. It is not effective or efficient to simply pour resources into regulatory compliance, instead manufacturers need to look at how they can eliminate the waste within the regulatory processes. This dissertation will look at the changes and challenges of regulatory affairs in the medical device industry and it will assess the suitability of lean tools for managing these challenges.

2 Chapter 2: Literature Review

This literature review will address a two research questions. Firstly, what impact is the current regulatory environment having on medical device manufacturers? It will look at how regulations are changing in recent years and the impact they will have on manufacturers. It will assess the impact of global regulatory harmonisation efforts. The second research question will ask what manufacturers can do to manage the current regulatory environment? It will look at the potential use of lean to manage regulatory compliance more effectively.

2.1 Overview of the current state of the Medical Device Industry

The Medical Device industry is estimated to grow from $228 billion in 2015 to a phenomenal $440 billion by 2018 (Cunningham *et al.* 2015). As there is increasing demand on the international medical device market, there comes an increasing demand on regulations. As outlined in the Introduction, there are have been significant changes to regulations in both established and emerging markets. Although a lot of these updates have been developed with the goal global regulatory harmonization, regulations are becoming more complex than ever and it is a challenge for medical device manufacturers to maintain compliance. In a survey completed by the Emergo Group on over 3,000 medical device industry participants, one of the key findings was that regulatory changes continue to represent the biggest business challenge.

Not only is the industry seeing massive growth due to aging populations and advances in emerging markets but there is also an emergence of new technologies that require these advances in regulation. For example, Additive Manufacturing, the broader category of manufacturing that encompasses 3-dimensional (3D) printing. Advances in Additive Manufacturing are already transforming the industry by creating devices that are customized to the patient's anatomy. Some of the more notable applications include craniofacial implants for reconstruction of the skull and facial skeleton, dental implants, joint replacements, and scaffolding for tissue engineering (Morrison *et al.* 2015). Additive manufacturing is already transforming patient care creating patient specific devices, however these advances in medical technologies are posing unique regulatory challenges. The FDA have issue a draft guidance document to outline their initial thinking on the technical considerations specific to devices that use additive manufacturing (*Technical Considerations for Additive Manufactured Devices* Draft 2016) but there is still a distinct need for more suitable regulatory pathways and regulatory guidance for 3D printed devices. Medical technologies are advancing rapidly but the regulations aren't as quick to adapt. The regulatory environment is evolving but it is not evolving at a fast-enough pace to meet the demands of the medical device industry. The new European Medical

Device Regulations are intended enable new technologies be introduced to the market in safe and timely manner (HPRA 2017). However, there a lot of unanswered questions on how the regulations will be enforced. For example, the Notified Body Operations Group (NBOG) only issued the first of draft guidance on the new regulations in August 2017 (*NBOG Report and News* 2017). The draft guidance is outlining how Notified Bodies will be designated. Manufacturers will need more guidance documents released if they are to comply with the new regulations before the transition period ends.

Regulatory Affairs (RA) is often viewed as a barrier or a burden, as a series of hoops that the manufacturer must jump through, and yet regulatory oversight is at an all-time high. QA/RA professionals consider that the European market will be difficult and unpredictable with the pending implementation of the new Medical Device Regulation (MDR), more stringent clinical requirements and the increased demands on Notified Bodies (Emergo 2017). The constant changing and evolving of global regulations makes RA one of the most unpredictable aspects of the medical device industry. Obtaining market approval in a timely and efficient manner is a key objective for manufacturers bringing a device onto the market. Market approval is only one aspect of a medical device's lifecycle. Manufacturers also must ensure they have systems in place to manage the post-market surveillance and vigilance requirements of each market. All regulatory bodies have the same end goal, to ensure devices are safe and effective, and perform as intended. Yet, the regulations are not aligned, requiring manufacturers to customize product testing and regulatory submissions to meet the specific requirements of each market. There are many efforts to harmonize regulations, but is this enough? Firstly, we will look at the harmonization efforts that have been implemented and the impact it has had on the industry.

2.2 Global Regulatory Harmonisation – the Regulator's Solution?

Bringing a medical device to market is a time consuming and costly process. This can largely be attributed to the lack of global regulatory harmonisation. The principle objective of global regulations is to ensure that all devices brought to the market are safe and effective to the patient and user, and perform as intended. Yet there are many discrepancies across safety and performance requirements and quality system requirements. There are many reasons for the differences in regulations. Countries have differences in priorities in their regulations and policies for health, environment, security and finance. Variances in legal system have a big impact on regulations. There may be specific issues or areas that regulators wish to address. Domestic interest groups may influence regulators to help shield them from international competition (Wiener and Alemanno 2015). Global harmonization of pre-market approval requirements will help minimize regulatory barriers. It will help trade among countries, promote technological innovation and access to technologies, it will reduce time to market and reduce the cost of regulations for the regulatory authorities and for the manufacturers (*Medical Device Regulations: Global overview and guiding principles* 2003).

The International Medical Device Regulatory Forum (IMDRF), formerly the Global Harmonisation Task Force (GHTF), was founded in 2011 as a voluntary group of global medical device regulators to accelerate international medical device regulatory harmonization (*International Medical Device Regulators Forum* 2016). The current IMDRF member states

include Australia, Brazil, Canada, China, the European Union, Japan, Russia, Singapore and the USA. The IMDRF are continuing on the work of the GHTF, whose purpose is to promote convergence of regulatory practices regarding the safety, effectiveness, performance and quality of medical devices; promoting innovation; and facilitating international trade through the publications of guidance documents (Tamura and Kutsumi 2014). The IMDRF's goal is to accelerate the international regulatory harmonization and convergence. But what impact has the IMDRF and GHTF made on the industry? Have their effort lead to a more efficient and effective process?

There are many areas that lack standardization in pre-market approval of medical devices, including demonstration of safety and effectiveness of the device; device classification; recognition of international standards; quality system requirements; and device submission formats. For the compliance with the essential principles of device safety and performance there is global guidance on the general principles applicable to all devices. Yet there is some ambiguity regarding more device specific requirements, such as electrical and software requirements ('Essential Principles of Safety and Performance of Medical Devices.' 2012). The IMDRF have published guidelines on device classification. Although most regulatory authorities have adapted the recommended risk-based approach, their interpretation of risk levels differs for each country (*Medical Device Regulations: Global overview and guiding principles* 2003, 'Principles of Conformity Assessment for Medical Devices' 2012, 'Principle of Medical Device Classification' 2012). The IMDRF have published the list of international standards that are recognised in the IMDRF countries. There is a large number of standards that are only partially recognised e.g. 33 in USA and 105 in Japan (*Final Report: List of International Standards recognized by IMDRF members as of March 2014* 2014). This is because authorities are bound to their regulations. Adopting these standards as recognized standards will be a big step towards global harmonization. Similarly, quality system requirements vary, therefore the manufacturer is required to demonstrate conformity through difference assessment routes and audit (*Medical Device Regulations: Global overview and guiding principles 2003 , Principles of Conformity Assessment for Medical Devices 2012*). When the manufacturer has met these requirements, they must compile the technical file to demonstrate conformity. The GHTF has published guidelines on the Summary Technical Documentation (STED) format. The IMDRF countries state that they will accept documentation submitted in this format (*Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)* 2008). The update to ISO 13485:2016, the international QMS standard for medical device manufacturers, also moves toward this STED format (*ISO 13485* 2016). However, some still have guidelines published on their preferred submission format, e.g. the US FDA (*Format for Traditional and Abbreviate 510(k)s* 2005). Manufacturer want to avoid possible submission rejections and therefore will follow each Regulatory authority's preferred submission format to ensure the submission will be accepted. Lack of standardisation leads to several problems such as inconsistencies in data and potential rejects due to conflicting or missing data. Is there more that the regulatory authorities can do to improve these areas? When the ultimate end goal is patient safety, what can the medical device industry do make global regulations more efficient and effective?

The Medical Device Single Audit Program (MDSAP) is an initiative driven by international Regulatory Bodies, where a recognized Auditing Organization can conduct a single Quality Management System (QMS) audit of a medical device manufacturer which would be accepted by multiple regulators. There are currently five Regulatory Bodies that are involved in the MDSAP program, including Australian TGA, Brazilian ANVISA, Health Canada, US FDA and Japanese MHLW. The three-year pilot program was initiated in January 2014 and was successfully completed in early 2017, with the program being formally initiated. Health Canada have announced that they will terminate their CMDCAS program in January 2019, and only accept MDSAP. This will put pressure on manufacturers to participate in the program if they wish to continue to sell their products in Canada. It is believed that a single audit program will benefit patient health by bringing medical devices to the patient quicker; it will enable regulatory resources to be leveraged; minimizes disruptions to medical device manufacturer by reducing the number of regulatory audits (IMDRF 2015, *The MDSAP: Easing the Audit Path for Quality Management Systems.* 2017, BSI 2017). Feedback from industry was positive and this is clearly a positive step forward in global harmonisation. However, it will more effective and more beneficial when more regulatory bodies recognise the program.

Outside of the IMDRF, regulatory harmonisation is evident. ISO 13485:2016, was released in March 2016 and there is a shift towards aligning global regulations. The Design Control formats including the Design History File and Design Transfer are aligning with US QSR (Quality System Requirements) and the STED recommendations. The risk based approach is also following the US QSR requirements. Although the improvements are evident, changes to regulations take time to be implemented. In 2012 the European Commission proposed a new revision of the regulatory framework. The new regulations were implemented in June 2017, with a three-year transition period for the MDR. The changes to the EU regulations are significant but it does show how much time it takes to implement significant changes. Instead of waiting for improved regulatory harmonization, the manufacturer needs to look at what they can do to manage regulations in a more effective and efficient way. In such a competitive market, manufacturers should not only be looking at innovative technologies but they should also be looking at innovate ways to manage compliance.

2.3 Overview of How Manufacturers Manage their Regulatory Strategies

As global harmonisation efforts take time, it is up the manufacturer to work with the cards they have been dealt. A smart regulatory strategy, along with strong project management is essential for manufacturers to overcome the challenges of global market access (Christen *et al.* 2009, Mir and Pinnington 2014). To optimize a market strategy, the manufacturer should have a clear understanding of the regulatory requirements for each market and use this information to their benefit. A manufacturer's global regulatory strategy must be aligned with the marketing and business strategy. In some countries, the registration process can take one to three years, therefore a three to five-year plan is best, tackling some markets in parallel. An effective and efficient strategy will avoid potentially expensive and time-consuming corrective efforts at a later stage. The first steps to develop a strategy are to know your target market, the resources required and reimbursement opportunities. The market approval that you are seeking first will be most time-consuming, as the testing and documents generated will be leveraged for other

applications. Therefore, looking at the larger markets is the most viable option as you will get the most return on your investment.

When a company is developing their medical device strategy they will typically go for approval in the larger markets such as EU and US. It is important to consider that the EU and US together account for roughly 70% of the global medical device market, so there is a huge amount to be gained to reach in to the other markets that account for 30% (Cunningham *et al.* 2015). Some of the other key markets to take into consideration are Asia-Pacific, Latin America and Canada. Asia-Pacific is emerging as a major leader and one of the fastest growing markets, taking 18% of the total market share. In particular China is emerging as the third largest medical device market (Cunningham *et al.* 2015) but it is complex, costly and time consuming to get market approval. China has a massive market share but it has a complex and timely regulatory framework, and China specific testing requirements. Russia is also a key market to pursue as its market share is rapidly growing, with it importing 60% of its medical devices and currently only 20% of the population have access to quality healthcare. It is a difficult market to get approval due to the complex regulatory requirements, the language barrier and the requirement for additional testing. The timing and timelines for market launches should be planned and monitored closely for an effective market strategy.

Early planning in the project initiation stage is critical to tailor a global strategy to gain market access quickly. Preparations for applications and approval timelines vary considerably for all markets e.g. FDA requires evidence of devices safety and efficacy but EU requires proof of safety and performance, therefore it can be quicker to get approval in EU first. However, targeting US approval first will give access to the largest medical device market. The best strategy would be start the applications in parallel but resourcing can be an issue here (Kwiatkowski 2013). Clinical evaluation requirements are an important aspect to consider, as they differ depending on the market. Some regulatory bodies do not recognise Clinical Trials completed in another region. As Clinical Evidence is costly and time consuming, developing a Clinical Strategy is important to avoid having to complete additional testing. Although regulatory requirements differ, there are efforts to harmonize the global approach among the top markets such as US, EU, Australia, Japan, China and Russia. Taking advantage of IMDRF guidelines will help streamline a strategy. There are some publications that outline alternative approaches to a regulatory strategy. Dr. Michael Drues published an editorial piece on the concept of competitive regulatory strategy, which is "defining a regulatory strategy to not simply to get a device on the market, but to also create a barrier to entry for the competition at the same time". Setting regulatory precedence for new devices at a high level, can it make it more time consuming and costly for competitors to bring a similar device to the market (Drues 2015).

When bringing a product to market, manufacturers often look on their market and regulatory strategies as standalone items but integrating regulatory and marketing within the project team will harmonise the manufacturers regulatory compliance. This is always difficult when there are so many other factors to consider. There are four key factors that are essential to meet the patient's need and are the foundation of a successful business: product quality, process efficiency, quality compliance and market access (Figure 1). There are many different functions

within a company, such as R&D, Operations, Quality, Regulatory, Human Resources, Supply Chain, Finance and Purchasing. Although each function has its own role, none can work as a standalone entity. A medical device manufacturer's primary function is to produce a product that meets the needs of patients but when a department's focus is solely on their own role, the department becomes a roadblock, rather than a collaborative system. It is easy for this to happen if departments are segregated rather than integrated as a project team. Take the QA/RA function as an example, by focusing exclusively on compliance to market access, process efficiency can suffer. Process efficiency is critical for a profitable business and a competitively priced product. Balance between the four focus areas is critical for the success of a medical device company. It is a constant battle for manufacturers to maintain this balance, as regulations are changing, patient needs are changing and manufacturing technologies are constantly evolving. There are many ways to manage and integrate these key focus areas. Process improvement is an area that receives a lot of focus in manufacturing, as this is area that drives profitability. There are many different tools that manufacturers use for process improvements, such six sigma and lean manufacturing. Six Sigma is a set of tools and techniques that are highly effective at improving the quality of the output of a process by identifying defects, eliminating their cause and minimizing the variability in the process (Dirgo 2005). While Six Sigma is a highly effective tool for improving process performance and improving product quality, it may not be a suitable tool for improving regulatory process. Six Sigma looks at identifying the defect and eliminating the cause. Regulatory requirements are dictated by regulatory bodies; the manufacturer cannot change the regulatory process. As outlined above, changing regulatory process takes a lot of time, so could lean tools be a way for manufacturers to improve how they manage regulatory compliance?

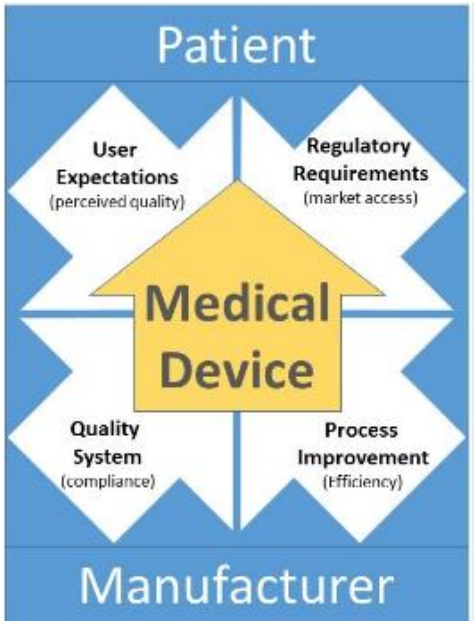

Figure 1: Four key focus areas critical for manufacture of medical devices that meet the patient's need (Yard 2016).

2.4 Lean Thinking – The Manufacturer's Solution?

2.4.1 Overview of Lean

Lean concepts were first developed in Japan after the second world war, when manufacturers could not afford massive investment required to rebuild facilities that were devastated during the war. Toyota manufactured automobiles following the "just-in-time" philosophy, that aims at producing only what is required, in the specific time, without unnecessary stock. It is a production method that uses less inventory, resources and investment; reduce cost and defects, while improving product quality (Bhamu and Singh Sangwan 2014). The term "lean" was coined by Womack *et al* in 1990 (Womack *et al.* 1991). There are many different definitions of lean across different researchers and practitioners. Some describing lean as a way; a process; a set of principles; a set of tools and techniques; an approach; a concept; a practice; a philosophy; and a system, to name only a few *(Bhamu and Singh Sangwan 2014).* Since then, lean has evolved and been defined in many ways, and is still evolving. A common definition of lean, is to produce higher quality products or services, at lower costs and reduced lead times, through the elimination of waste (Cherrafi *et al.* 2016).

2.4.2 Lean Principles

Lean principles have transformed manufacturing by producing higher quality products and services by lowering costs and lead times by eliminating waste, or *muda* (Cherrafi *et al.* 2016). *Muda* is the Japanese word that can be translated as "wastefulness". *Muda* used to define waste, or more specifically any human activity that absorbs resources but creates no value (Womack and Jones 2003). Lean looks at ways to eliminate waste, or these "non-value added" steps. The seven forms of *muda* are transport, inventory, motion, waiting, over processing, overproduction, and defects (Womack and Jones 2003). Refer to Figure 2 for a description of each type of waste. Regardless of the process, be it a production line or a supporting service, or business process, the types of waste are quite similar. Figure 3 compares the types of waste found in a production process and business processes. Business processes are considered the processes that are required to support a business, outside of the production line. RA processes can be described as business processes. Table 1 gives examples of each form of waste that may be found in a business process, most of which can be applied to RA. These forms of waste are non-value added operations that have a direct impact on performances, quality and cost. *Lean thinking* is a term coined by James P. Womack and Daniel T. Jones as an antidote to *muda* or waste. Lean thinking is a way to outline the value of a process, to complete value actions in the best sequence, and to conduct these actions without interruption and as effectively as possible, i.e. do more, with less and less (Womack and Jones 2003).

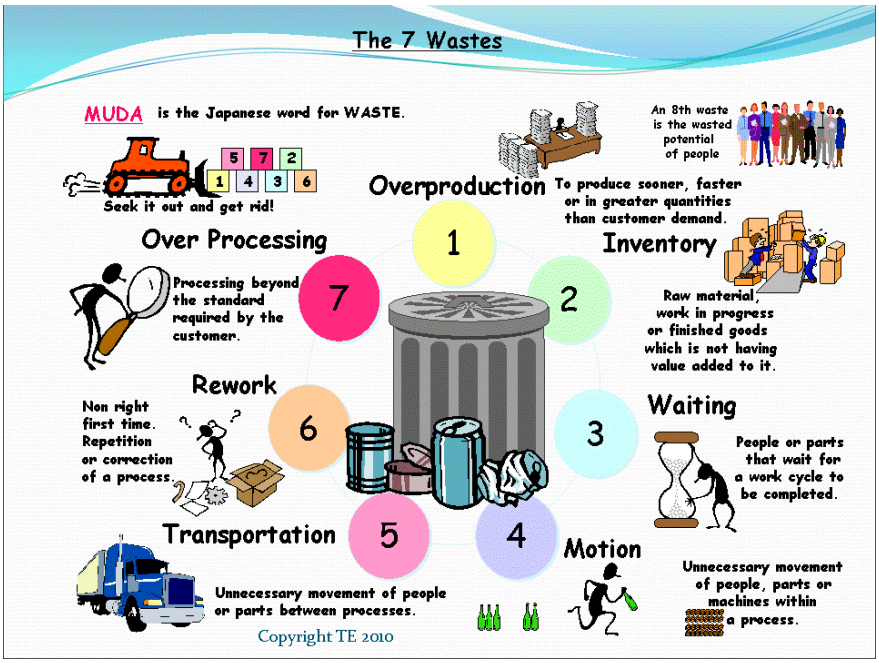

Figure 2: Types of Muda (TE 2010)

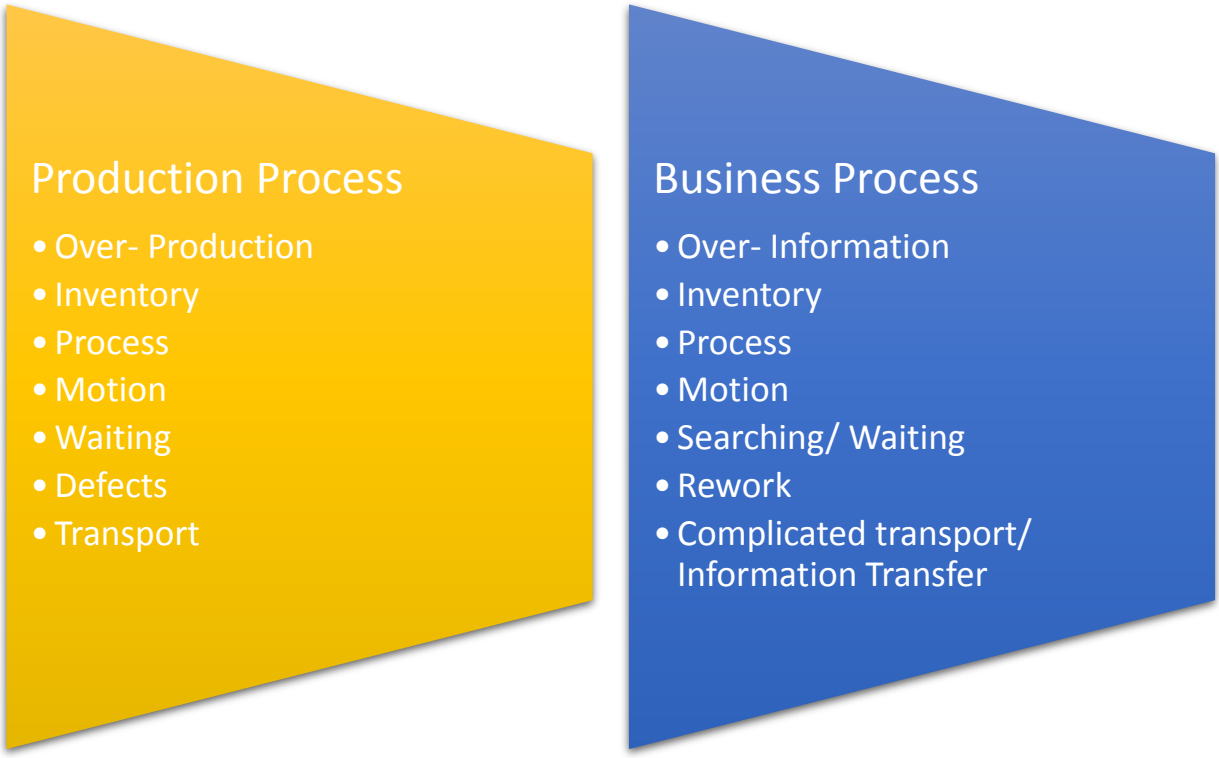

Figure 3: examples of waste in Production and Business Processes

Table 1: Examples of waste in a Business Process	
Over information	• Tasks not clearly defined • Too much detailed information • Senseless tasks, double-work, reporting • Emails • Unnecessary participation in meetings • Waste of materials
Inventory	• In and Out trays, written communication, pending tasks • Personal data management, office supplies • Archiving/filing • Waste of space
Searching/Waiting	• Contact persons, waiting for working materials and appliances • Waiting for input from upstream process (decisions) • Waiting for working materials, office supplies, colleagues, late meetings • Inefficient utilization of electronic media • Pending signatures • Inconsistent structure for data storage
Complicated Transactions/ Information transfer	• Transferring information, distribution of information by making detours • Time/transport to meetings
Process	• Computer program shuts down • Missing or not adhered to meeting agendas, wrong participants in meetings • Over or under information, badly prepared meetings or conference calls. • Changes of priority, missing rules, bad planning of process steps • Missing process standards • Insufficient leadership (tasks not clearly defined, unclear responsibilities)
Rework	• Wrong decisions, wrong interpretation of rules, guidelines and agreements • Partial or wrong information • Inquiries due to poor quality information
Motion	• To printer, other offices. • Disarrangement, suboptimal workplace layout • Office/work place location

The five principles of Lean thinking are *value, value stream, flow*, *pull* and *perfection.* Lean thinking starts by defining the *value* accurately i.e. the specific product or service that the consumer needs. Next, the *value stream* is defined; which is the set of actions required to bring a product/service through concept to the end user (Rother *et al.* 2003). These actions can be broken down into three categories of value added, non-value added and necessary non-value added. Value added process steps are steps that adds value to the product/service. Necessary non-value added are steps that is essential to the process but does not add value to the product/service. Non-value added are steps that are not essential to the process and do not add value to the product/service. Eliminating the non-value added steps, removes the waste from the process and allow the manufacturer to create a single-stream, continuous *flow* of only value-

creating steps and necessary non-value added steps. Flow is optimised by making improvements in the process, either through *kaikaku* "radical improvement", or *kaizen* "continuous incremental improvement". Developing a good *flow* in a process means that the time spent on a process step is kept to the shortest time possible. Figure 4 outlines the difference *flow* can make when introduced on a production line. Introducing flow will reduce cycle times and increase productivity, thus creating a *pull* on the product/service. The concept of *pull* benefits the customer, they only take what is needed, when it is needed, avoiding waste. As per Figure 5, these key principles feed into a cycle of continuous improvement, with the goal of *perfection (Womack and Jones 2003). Kaizen* and *Kaikaku* are only two of lean tools that manufacturers can use. Successful implementation of lean should employ the use of different tools and techniques in tandem.

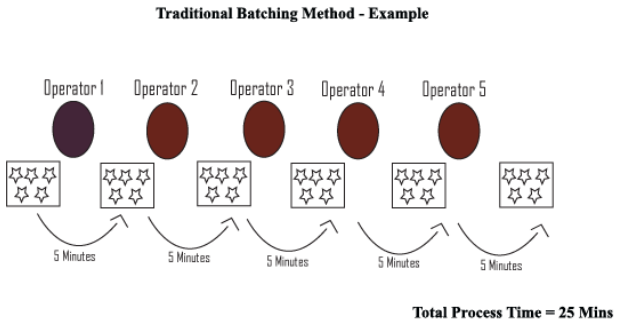

Figure 4a: Production line following traditional batch manufacturing (Lean Flow 2017).

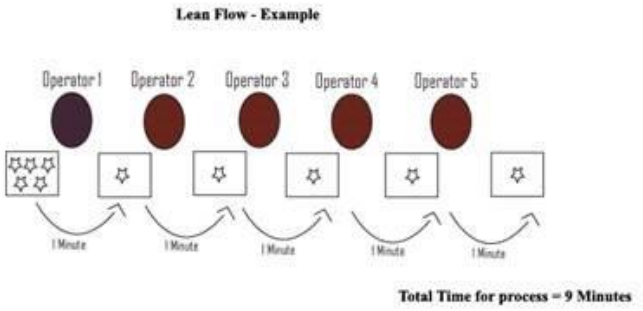

Figure 4b. Lean production line single-stream continuous flow (Lean Flow 2017).

Figure 5: The continuous cycle of the Five principles of Lean Thinking (Womack and Jones 2003).

2.4.3 Lean Tools

There are many lean tools and techniques used in lean applications such as just-in-time (JIT), Kanban, Standard Work, Kaizen and Continuous Improvement, Value Stream Mapping (VSM), 5S and Visual Management. As the concept of lean was first established with Just-in-Time philosophy, it shall be addressed first. Lead time is defined as the time it takes from initiating to completing a process. The lead time of a process dictates everyone's workload, including RA. The RA can reduce the time it takes to complete a process, it frees up resources for other tasks, it enables RA to respond to queries quicker, it reduces cost and it makes the organization more competitive. Just-in-Time (JIT) is a general principle that is adopted to reduce lead times (Ward 2006). There are many ways to achieve JIT. Kanban is a common method used to achieve JIT. Kanban is a system that regulates and simplifies the flow of materials into a process. It is a Japanese term that can be translated as "billboard" or "signboard". (Marek and Łukasz 2017). It is a system that used to establish the pull on the process, with "pull" being one of the core principles of lean thinking. The system works in many ways. Kanban visualizes the work flow. Kanban also limits the work-in-progress (WIP), as the WIP is determined based on customer request and the work item is only pulled through the process if there is capacity in WIP. To have a Kanban system that works, the workflow must be understood so that the process flow it driven by requirement and target completion dates, which in turn will establish the start date of the process. This allows the work flow to be controls. The implementation of feedback loops is key to successful implementation, as the system needs to be able to adapt to change and needs to be able to prioritize work items bases on business needs and customer needs (Al-Baik and Miller 2015, Marek and Łukasz 2017). There are many advantages to using Kanban. It improves control of the process by supports problem solving and decision making. It is a visual aid for co-ordinating work loads of cross-functional teams. Control of the WIP, means the lead time of the process is reductions. As the system is driven by customer needs, customer satisfaction is increased. When the process is leaned out and visual aids are put in place, the defect rate is reduced and product quality improves. As it highlights any defects or inefficiencies in the process, it facilitates the continuous improvement strategies. There are challenges, as there needs to be a strong understanding of lean principles and the process flow needs be clearly mapped out with defined metrics (Al-Baik and Miller 2015). There are many publications on the use of Kanban. It is not limited to the manufacturing lines, it is used across many types of processes and services. For people working in RA, they are faced with managing many tasks, with strict deadlines. The Kanban system could be an excellent tool for RA to visualise and manage the flow of their workload, and employ the JIT approach, ultimately reduces lead time and resource requirements. JIT is not a standalone tool, it is achieved using different tools and techniques.

A critical element required for lean to work is standardisation of the process. Lean does not work if people a choose their own method or sequence of work. If there are variations in the process, the outcome becomes unpredictable and continuous improvements are not manageable. To standardise a process, their needs to be an in depth understanding of how the process works. It must be documented in detail with the support of visual aids. Root cause analysis should be completed on the process variations, as this will help to resolve the issues

when mapping out the future state. Some of the key components to consider when standardising a manufacturing process include the capacity of the cell, the cell layout, the flow of material, work responsibilities, and staffing levels. Understanding what the process is capable of will allow the flow of the process to be balanced and the takt time to be defined i.e., the time needed to complete the process to meet the customer demand. If a process is stable and standardised the problems become more visible. Standardisation facilitates problem solving and helps improve the workflow. It is the baseline for continuous improvement. Lack of standardization is one the main reasons failure of lean projects (Whitmore 2008, Johansson *et al.* 2013).

There is a key relationship between standardisation and Kaizen. Kaizen is process-oriented. Focusing on the process and making improvements to the process will inevitably improve the results. Then maintaining the process through standardisation will achieve lasting improvements. Kaizen translates as "continuous incremental improvement" (Womack and Jones 2003) but it is also simply mean improvements. In a broad sense, Kaizen and continuous improvement go hand in hand (Imai 1986). Masaaki Imai describes Kaizen as a customer driven strategy for improvement and that improvements to quality, cost and scheduling will lead to increased customer satisfaction (Imai 1986). If we look at this in terms of Regulatory Affairs, the Regulatory Agencies can be described as the customer. Improvements to the quality and timeliness of the work will lead to increased satisfaction of the regulatory bodies. Kaizen is a people oriented process, it should involve personnel from all levels within the organisation. Top management must support the process and dedicate the necessary resources. The people that work in the processes are critical, as they know the process better than anyone else and need to understand how kaizen will benefit the process (Anders 1997). Kaizen is usually implemented as part of a focused and structured project, that uses cross-functional teams. It focuses on a specific area, with specific goals. Kaizen projects often result in a reduced lead time, simplified WIP and increased productivity. As Kaizen projects engage all levels of personnel, it helps employee engagement and improves morale (Eileen *et al.* 2010). Kaizen does not look to change the process, instead it looks at removing the waste from process. Therefore, it is an ideal tool for regulatory processes. It uses many different tools for process analysis and problem solving e.g. process flowcharts, 5 whys, cause and effect diagrams, pareto charts, value stream mapping, standard work and 5S. Kaizen events follow as standard format, typically over a three to five-day period. There is a format follows as a sequence, starting with lean training to refresh people on lean principles. Then the event focusses on the process, by mapping out the current state. At this stage, it is beneficial to identify the value added and non-value added tasks. After this the team look at different areas for improvement, using root cause analysis tools. Then the team can focus on areas for improvement, map out the future state and if possible, implement the actions. The results must always be presented to the wider teams so that everyone will understand the decisions and support the change. If the process cannot be implemented immediately, action items must be assigned for the follow up activities (Eileen *et al.* 2010). The core principle of lean is continuous improvements and Kaizen is the best tool to achieve this. It promotes a problem solving culture, reduces process waste and optimizes productivity (Cherrafi *et al.* 2016).

Standardisation and Kaizen are used to create a lean process. Value stream mapping is a tool used to support Kaizen and Standardisation. The value steam is all the actions, both value added

and non-value added, required to bring the process from initiation to the customer. Mapping out the value-stream is a visual representation to see and understand a how materials and information flow through the process. Value-stream mapping does not just focus on individual processes, it looks at the bigger picture. This is important for regulatory processes, as there are so many processes linked and dependent on RA. Value-stream mapping is an essential tool as it is a visual aid to help identify waste; it provides a common forum for discussing the collective processes; it aids decision making by clarifying the links between processes; it shows the link between the flow of material and information; and it forms the basis for an implementation plan. The best thing about a value-stream map is that it is a qualitative tool, that helps describe how the organisation needs to operate to create a flow (Rother *et al.* 2003, Womack and Jones 2003).

Implementation of lean is a challenge, but maintenance of lean is the biggest challenge. Visual Management Boards are 5S are popular tools used to support the implementation and maintenance of a lean philosophy. Visual Management Boards should be used in conjunction with kaizen, standardisation and Kanban as a communication tool. Communication boards help guide team briefings and steer personnel in their activities. They assist in understanding a situation in a glance, exposing problems, promoting improvement. The layout and content of the boards should be carefully considered to optimise the impact of the boards and the quality of data (Bateman *et al.* 2017). 5S is an acronym for sort, set in order, shine standardise and sustain. Refer to Table 2 for a breakdown of each of the 5S It is an effective but basic lean concept used to prevent a company from going back to its old ways (Omogbai and Salonitis 2017). It establishes the operational stability needed for maintaining the philosophy of continuous improvement. It is proven to improve efficiencies and performance by creating and maintaining a well organised, clean and high quality work space (Marascu-Klein 2015). It is most often used to organise and maintain a physical working environment, but it is equally effective to use in a digital space as well to organise documents and folders (Gomes *et al.* 2013). There is a lot of data published on the effectiveness of using 5s in the work environment to maintain a lean process. It would be ideal for use in RA, to assist in standardisation of files, folders and even product submissions.

Table 2: 5S acronyms (Omogbai and Salonitis 2017)	
Sort	Organise things in order, for ease of storage and retrieval
Set	Designate and label storage area i.e. a place for everything and everything in its place
Shine	Keep everything clean and tidy
Standardize	Document the standard for the area and implement a plan to main the standard
Sustain	Maintain the standard and form a habit of continuous improvement

2.4.4 Application of Lean

In a literature review completed by Bhamu and Sangwan, a total of 209 research papers on lean manufacturing were reviewed. The critical factors for successfully lean implementation include leadership and management, financial backing, lean skills and expertise, strong performance and acceptance of lean culture in the organisation. Some of the common reasons for failures in lean implementation include the use of wrong tools to solve problems, lack of understanding of lean, and bad decision making skills. However regardless of the size of the company, the ones that used the tools appropriately seen improved lead times, improvements in quality of product, reduced scrap and defect rates and improved customer satisfaction. Education and training are key, as the most common reason for failing to implement or maintain lean processes is poor understanding of lean management from both management and employees (Bhamu and Singh Sangwan 2014). This review and other reviews have found that large manufacturers were more likely to implement lean than small and medium enterprises (SMEs) (Qing *et al.* 2015). There is hesitation in SMEs to implement lean for fear of cost implications and project failures. As there is little data or no data on the use of lean tools for regulatory process, companies may also be hesitant to implement lean due to the same fears.

There is no standard lean implementation framework used in industry. Each company can manage their lean programs differently. Regardless of the approach to lean, if the tools are used in the correct way, the company is on the correct track. Before implementing lean, the company should do their research and gain an understanding of the challenges that they may face. Before initiating the lean program, the first step is to generate a lean awareness plan for all employees, with different levels of training depending on the role in the company. The next step would be to ensure that the objectives are clearly outlined with precise data on the process. Support and input from management is key, as they are the decision makers. They must ensure that there are no barriers. As lean philosophies are always customer focused, the needs of the end users must be the driver of the new process. During the implementation, the main aim is to eliminate all forms of waste, to improve performance. The implementation of lean is the easier part of the process. Maintaining the effectiveness of the process is often the biggest challenge, as it must be a cycle of continuous improvement. Implementing a continuous improvement plan can help overcome this (Jaiprakash and Kuldip Singh 2014).

2.5 Literature Review Conclusion

The literature reviewed in this dissertation was completed across many industries, e.g. electronics, automotive, food and beverage, service sectors, and health sector. This shows that regardless of the industry, product or service, lean is an excellent tool to use. The automotive industry is the best example for lean success. Even though it may not seem like a comparative industry, the automotive and medical device industry have many similarities. They are both highly regulated, with strong emphasis on risk, and they both deal with complex, customized products to be sold in customer driven and competitive markets. Regardless of the complexity of regulations and variety of processes and products associated with regulatory affairs, if implemented and maintained correctly, lean is an excellent tool to use to improve the quality of data and reduce the time and costs associated with regulatory processes. Unfortunately, there is very little data available on the use of lean to improve compliance and regulatory processes.

Lean is often used in conjunction with compliance but there is little evidence of it being used to improve the process of compliance. In the context of a production line, the RA and compliance tasks would be considered a necessary *non-value added* action. But it is incorrect to view RA in this context, as the RA tasks could be considered standalone processes. Looking at the RA task as a process, the *value* and *value stream* can be identified, making it easier to create a *flow* and *pull*. There numerous types of regulatory processes that include change control assessment, the generation a technical file; submitting a change to a Notified Body; implementing new/updated regulatory standards; and changing an Authorised Representative; to name only a few. As with any process, waste, can be identified in a regulatory process, be it rework, waiting, over-information or duplication of work. This dissertation will explore why lean is not an accepted approach for improving regulatory processes; it will explore alternative methods that manufacturers are using to manage the challenges of the regulatory compliance in the medical device industry; and will look at how lean tools can be used to eliminate waste and optimize regulatory processes.

3 Chapter 3: Methodology

3.1 Methodology Introduction

Ultimately, Regulatory Bodies define regulations and regulatory submission requirements, therefore, much of this is out of control of manufacturers. Manufacturers are facing greater challenges of managing complex and varying regulatory requirements. Therefore, they need look at ways to streamline and optimize how they manage and co-ordinate these requirements. There is ample evidence on how lean tools can significantly improve the effectiveness and efficiencies of manufacturing processes. Yet, the literature review in Chapter 2, identified a gap in research on the use of these tools to improve regulatory processes. The research has shown that lean tools can be applied to any process, be it a production line or a business process. Despite the data being mostly positive, there is very little acceptance of the use of lean for improvements to regulatory processes. This dissertation can address the gaps in research data. By comparing opinion, theory and practice, this research will address the following objectives:

A. Identify how manufacturers perceive current regulations and if they identify a need to improve regulatory processes.
B. Determine if manufacturers are using alternative methods within their companies to improve/streamline processes.
C. Explore if lean tools can be used in regulatory processes.
D. Evaluate whether lean tools are suitable for regulatory processes.
E. Formulate ways in which lean tools can improve regulatory processes

This chapter will indicate how these objectives will be addressed, outlining the research strategy; how the data will be collected and analysed; and any limitation or potential problems with the strategy.

3.2 Research Strategy

Several research strategies that will be adapted for the purposes of this study. Firstly, Objectives A to C, will establish manufacturers perception of the need for improved processes; gain an understanding of manufacturer's experience with lean; and explore manufacturer's opinions on the use of lean tools for regulatory processes. These objectives will be addressed through a series of interviews with people that work in regulatory affairs with varying levels of responsibility and experience; and, people with experience with use of lean tools in the medical device industry.

Objectives D and E will be addressed through case studies to gain an in-depth look at how companies can adopt lean strategies for regulatory processes and review similar models that are currently used in industry. A sample of lean case studies will be reviewed to give quantitative data to demonstrate the benefits of using lean tools to improve compliance processes. The research will aim to establish if lean tools can be used eliminate waste, optimize value-added activities, and shrink lead times for regulatory processes.

3.3 Data Collection

One of the aims of this dissertation will be to establish if lean tools can be used to eliminate waste, optimize value-added activities, and shrink lead times for regulatory processes. Quantitative data is used in lean processes to quantify the improvements. Quantitative data will be gathered as part of this dissertation, however there are restrictions. There are many variables in all regulatory processes, there are limitations in how the quantitative data can be compared. For lean to work, it needs to be embedded into the culture of the company. People's attitudes and perception of lean are a major factor with lean implementation. People's opinion, recognition of the need for change, commitment, and openness to change are critical for the success of any lean project. As it is difficult to quantify people's opinions and perceptions, without extending the study to a wider group of people, qualitative data will be used to investigate the human aspect of lean implementation.

The mixture of qualitative and quantitative data will be collected in the following ways:

- Qualitative data will be collected through interviews that will establish opinions on:
    - the state of industry,
    - challenges of regulatory,
    - the benefits of lean,
    - the use of lean in regulatory affairs,
    - any examples of lean activities or innovative methods within a company.
- Qualitative and Quantitative data will be collected through case studies:
    - Examples of lean tools used to improve compliance/quality/regulatory processes
    - Example of a company that has developed a tool to reduce the costs and time associated with product registration.

3.3.1 Interviews

Interviews will be completed following a semi-structured format. They will be conducted to get an understanding of people's perception of the RA industry, if they identify a need a to change how processes are manages and to gather opinions on the use of lean tool for regulatory affairs processes. As opposed to survey's, interviews cannot be completed on a representative sample size of the population. Therefore, the choice of interviewees will be stratified, representing personnel involved in different levels of RA and Lean work. Refer to Table 3 for interviewee selection and rational for selection. The interviewees will be contacted with a general guide of topics to cover and number of questions will be pre-prepared by the interviewer to ensure all topics are addressed.

Table 3: Interviewee Selection

Whom?	What?	Why?
RA Managers/ Directors	Management perspective	Understand the point of view from the decision makers
	Opinion on lean	Buy in from management is key for the success of lean.
	Opinion on the industry	What is the perception of the current state of regulations? Are regulations quick to adapt? Are regulations becoming smarter or more complex? Is there a need to change how we work?
RA Specialists	Overview of day to day RA work	Understanding of the day to day work to establish areas for potential use of lean tools.
	Is there a need for change?	Is there a crisis or a burning platform?
	Are RA departments innovative?	Is there a need for lean? Are companies adopting innovative ways to manage RA activities?
	Opinion on lean	Is there an understanding of how lean works? Is lean suitable for RA?
CEO of RA Consultants	Consultant perspective	Point of view of leader in industry, that changing and improving the way RA works
	Overview of RA management platform	Why was the platform developed? How does the platform work? What are the challenges of implementing the platform? What impact has the platform had on the business
	Opinion on the industry	What is the perception of the current state of regulations? Are regulations quick to adapt? Are regulations becoming smarter or more complex?

Table 3: Interviewee Selection

Whom?	What?	Why?
		Is there a need to change how we work?
Lean Manager	Overview of Lean	Why should a company use lean tools?
	Use of lean in business processes	Is lean suitable for business processes? What are the challenges with using lean tools in business processes? Tips for a successful lean project.
	Opinion on using lean tools for RA processes	Is lean suitable for regulatory processes?

3.3.2 Lean Case Study

VistaMed is a leading provider of complex extrusions, finished catheters and devices to the minimally invasive medical device industry. VistaMed specialises in providing design and manufacturing expertise from concept development to finished product, for a wide variety of extrusion and catheter based medical devices (*VistaMed - Innovative Catheter Solutions* 2017). Since 2010 VistaMed have been partnered with Freudenberg Medical, a medical device manufacturer with a strong lean philosophy. Freudenberg Medical have developed a proprietary process called "GROWTTH®", which stands for "Get Rid of Waster Through Team Harmony" (*Freudenberg Medical - Growtth® Our Lean System* 2017). Its aims to eliminate waste, optimize value-added activities and reduce lead time throughout the processes. Each of the eleven global Freudenberg Medical sites have implemented lean processes throughout the companies. This dissertation will look at how VistaMed have used lean to improve business processes that are relevant to the product lifecycle. This case study will look at how these lean tools can be used to improve compliance and regulatory processes.

3.3.3 Arazy Group Case Study

Arazy Group Consultants Inc. is an international regulatory consultancy company with over 20 years' experience in the medical device and in-vitro diagnostics (IVD) industry. Almost 10 years ago, Arazy Group first came up with the concept of developing a tool to manage the complexities of handling multiple product registrations in an effective manner. Thus, Licensale was introduced to the market in late 2012. Licensale is an online customized management software, integrated with a network of regulatory experts, to optimize, plan, control and resource the entire regulatory life-cycle of a product (*Licensale* 2017). Arazy Group have combined the power of raw data, the efficiency of data management, and the connectivity of a professional social network into a new technology service platform and launched an integrated suite of cloud-based products designed to streamline, simplify, and expedite international regulatory affairs. This dissertation will look at Licensale as a case study to see at what one company is doing to overcome the challenges of dealing with complex regulatory processes. The study will look how Licensale works and at the impact it has had on Arazy Group's customers. The study will compare the Licensale process with the standard product registration lifecycle and establish if other medical device companies can adapt similar thinking to make improvements in their own processes, using lean tools.

3.4 Framework for data analysis

The interviews will get in in depth opinions on a small group of industry representatives. Before looking at how lean can be implemented, it is important to gain an understanding of typical day to day work that an RA professional completes. Unless there is an understanding of the details involved in typical RA tasks, it cannot be established how lean can be implemented. The opinion of management is critical, as they are the decision makers and people who need to drive the change. Speaking to people with experience in the industry, will give an understanding of how the industry has evolved over the last few decades. As there are examples of where lean has not obtained desired results, it is important to speak to people with experience in using lean tools. Speaking with people from different types of companies, different levels of responsibilities and varying experience in the industry, the data will be reviewed to establish if there are common opinions across each interview. It will identify areas for concern and areas for improvement.

The VistaMed case study will analyse the tools that are suitable for business processes with particular focus on compliance related processes. These will be processes that RA and other departments within a company are involved in. These case studies will be representative of a typical working environment, as RA have a unique role in a company, where they cross over to many different departments. The Arazy Group data will be reviewed to establish if the Licensale application does save money and time for its customers. The data from Arazy Group will be compared against published data and studies where possible. The case study will use lean tools to explain how Licensale has improved the process. It will assess if manufacturers can adopt a similar approach.

3.5 Limitations and potential problems

As lean is a culture and there is a lot of psychology behind lean, an interview is more beneficial than a survey, as it is easier to get an understanding of people's opinions and perceptions of the topic in an interview. A survey would make it possible to gather quantitative data but in this situation, interviews will be more beneficial. The interview will allow for detail discussions on specific topics, that a survey or questionnaire would not allow. Although it will not reach large number of participants, using an interview will get a more focused opinion from a small group of people. The choice of interviewee is important to get the point of view of peoples with different levels of experience and different levels of responsibilities. Selecting interviewees from different types of companies, in locations around the world, will also assist in getting different opinions. The potential for influence is a factor to be considered when completing interviews. The interviewer must not lead the interviewee to a certain way of thinking. Interviews must be completed without bias.

The VistaMed case studies looking to quantify how lean can change a compliance or regulatory process. Due to restrictions within the author's current role, it will not be feasible to focus on lean projects that are solely regulatory processes. To overcome this, the selected case studies will look at compliance related process that most RA professionals would be involved in. As the author will be participant in some of the case studies, the objectivity can be questioned. This will be avoided by using strong research and not focusing solely on work-based results. It can be questioned if the project will be representative of a real working environment. Using specific

lean case studies that were within the constraints of a typical manufacturing compliant environment, will give a realistic side to the project. Also, instead of focusing on one sole project using one type of lean tools, there will be multiple case studies completed using different lean tools. For the Arazy Group case study, there may be limitations in the data received. This data must be reviewed objectively and compared with published data where possible. If there is no data available to verify information, then this should be highlighted, to ensure an impartial assessment of the data is completed.

As with any chosen research strategy, the limitations and potential problems have been identified. It is important that these limitation and pitfalls have been addressed, to show an understanding of the chosen strategy; to act as a reminder of certain traps to avoid; to highlight ways to overcome the limitations; and to also aid the choice of research strategy for any future studies expanding on the topic.

4 Chapter 4: Findings and Results

4.1 Interviews

4.1.1 Lean Perspective – Use of Lean in Business Processes

Seamus Maguire, the Lean GROWTTH Manager at VistaMed, with 10 years' experience in Lean Systems and certified with a Lean Systems Black Belt, see the benefits of using lean systems every week. VistaMed, a contract manufacturer, is leading provider of complex extrusions, finished catheters and devices to the minimally invasive medical device industry. VistaMed first started using lean tools in 2010. As a company that has grown 30% each year for the past three years, the use lean tools have helped strengthen the company. Having ran many Business Process Kaizen events in VistaMed, Mr. Maguire sees how effective they can be as "a huge portion of overhead costs in any manufacturing facility are the business processes, so there is huge opportunity to get rid of waste". It is much easier to quantify the effectiveness of a shop floor Kaizen. Yet regardless of whether it is a Kaizen on the production line or a business process, the goal is the same, to reduce costs and to reduce lead time. There are a few ways to reduce lead time, such as removing the non-value added items or by using Little's Law, which looks at reducing the amount of work in progress to reduce the lead time (Figure 6).

$$\text{Average Lead Time} = \frac{\text{Average Work in Progress}}{\text{Average Throughput}}$$

Figure 6: Little's Law

As with shop floor Kaizens, business process kaizens follow the same format. The process is mapped out and each step is analysed, as to whether it is value added or non-value added. A future state map is then created based on the regulations. Mr. Maguire gave an example of a recent Kaizen he was involved in that looked at Preventative Maintenance for equipment. Based on the regulation, the future state map had 4 steps. First step was to create a unique identifier number for the equipment. Second step was to create a record that defines all the maintenance

requirements for the equipment. The third step was to complete the maintenance on the equipment. The fourth and final step was to document and sign that the maintenance was completed. For a business process Kaizen, the process needs to be compliant with the regulation but it also needs to avoid adding additional information. People often to want to overcomplicate with more details. Although it may seem counterintuitive, adding more information ends up creating more opportunities for error. Mr. Maguire says "You are either compliant with regulations or you aren't. When you go beyond the requirements and the regulations, you create these opportunities for error, which can lead to non-conformance and leads to CAPA. People put a "fix" in place with additional checks, without completing a proper root cause analysis and properly addressing the problem. You have ended up adding an extra check without eliminating the error. It is a vicious cycle that is hard to get out of. Ultimately you need to be compliant, with the minimum amount of work and minimum amount of resources to effectively do that task. And that is where lean comes in" (Maguire 2017a).

When asked about the challenges of implementing lean, Mr. Maguire finds that people being resistant to change can be a big one. He can empathise with this because people are often very invested in a process they work in. He would look on resistance to change as good thing, because it usually means people care about the process. There are many ways to overcome this resistance, and change people's attitude. If there is a crisis, or what is called a "burning platform", this can help get people on board. A crisis is a situation that everyone knows needs to change. An example of a crisis that Regulatory Affairs departments are facing now could be the new Medical Device Regulations coming into place. The crisis could be the potential for devices to be withdrawn from the market; or lack of resources to address these changes. For a company to stay compliant and competitive, lead times need to be shorter. The Kaizen format is also important for getting people on board with the changes. Mr. Maguire always structures a Kaizen so that the first day covers training on lean systems, with test simulations to demonstrate how it can be effective. Next, the team will walk through the process backwards, ensuring all details including minor steps are fully mapped out. Then the future state is mapped out ensuring all the applicable regulatory requirements are addressed. When the process is broken down into every detail, then compared with the regulatory requirements, it can change people's opinion on how the process should work (Maguire 2017a).

However, it is not easy to implement lean. A common pitfall would be selecting the incorrect Kaizen team. It is essential to have people that are part of the process and to have people that can make the decisions. Another pitfall is not dedicating enough time to the Kaizen, as the changes should be implemented before the Kaizen event ends. Mr. Maguire uses the "standard wedge" analogy to explain this concept (Figure 7). "Imagine you were pushing a ball up a hill, just like making improvements. If you put the pressure off, or let go of the ball, you roll back. But if you stick a wedge in, a standard wedge, by updating docs with the new process, it is going to stick" (Maguire 2017a).

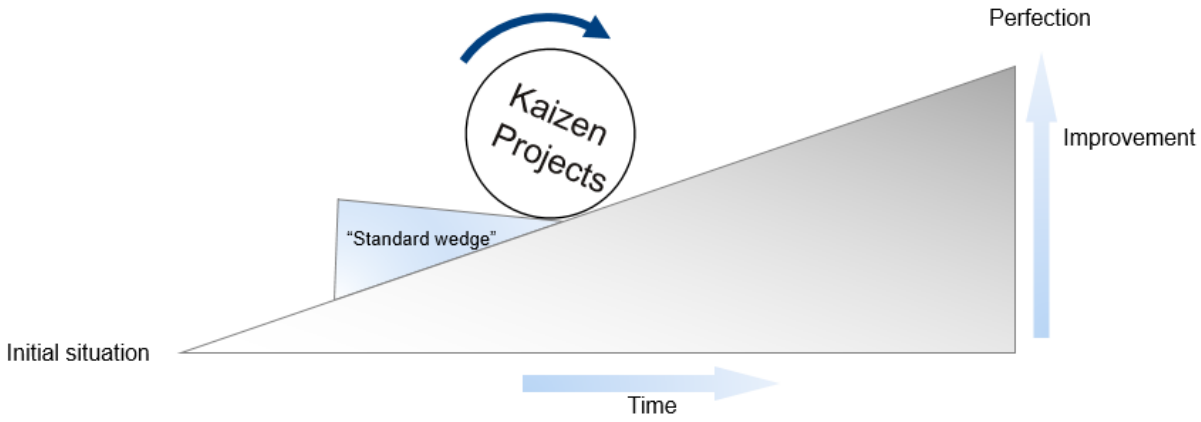

Figure 7: The "Standard Wedge"(Maguire 2017b)

The hard work doesn't end after the Kaizen event is over. Lean is based in a principle of continuous improvements. Ideally, Mr. Maguire tries to revisit each area every 6 months, "there is waste in all processes, so you can always make improvements to eliminate waste". In regulatory, it is easy for a process to change or drift, so lean must be embedded into the company culture. When new regulatory requirements are being implemented always use lean tools to generate the future state map incorporating the new regulations. The process can also drift because of a submission rejection or an audit finding. Mr. Maguire sees root cause investigation as key to identify the true problem and to avoid introducing waste to the process. In Mr. Maguire's experience "if I was to look at any audit findings, it is the same things that come up time and time again. That is evidence we are not getting to root cause. If you are truly getting to the route cause and put the proper fix in place, you will never have that error again" (Maguire 2017a).

An important aspect of lean, is single piece flow. Working in RA, there is so much dependant on external factors and so many independent tasks that need to come together. How can single piece flow work for regulatory processes? Mr. Maguire clarifies that "the idea with single piece flow is that you work one thing at time". In regulatory there are often situations where multiple reports/documents/submissions are required at one. Instead of working on them all at one time, focus on the item that can be finished first. If that item gets put on hold, move onto the next, but return to the first whenever possible. "We should always be trying to get one project further in the process. Business process improvements are always about shortening the time of getting the process from start to end" (Maguire 2017a). When planning for single piece flow, identify the constraints in the process, then work the timelines around these constraints.

There are many challenges with implementing lean systems, especially dealing with complex and sometimes contradictory regulatory requirements. Mr. Maguire does acknowledge that it is difficult to implement lean systems, as "lean is very much about exposing problems and waste and often people don't want to deal with that". However, he is confident that the company that uses lean tools in their regulatory processes will have the competitive advantage and quicker time to market, when compared to companies who don't use lean. Lean implementation does require resources to deal with the problems. It can be difficult to pull these resources but it pays

off in the long term, with a quicker and more cost-effective process. Regardless of whether it is a production line, a business process or regulatory process there will always be waste and therefore there will always be opportunities to eliminate waste. The same lean principles can be applied regardless of the type of the process. VistaMed understand the benefits of a having a lean system and have already used lean tools to improve compliance within the company. As a contract manufacturer that offers regulatory support to their customers, the company is equipped with expertise to implement lean regulatory processes.

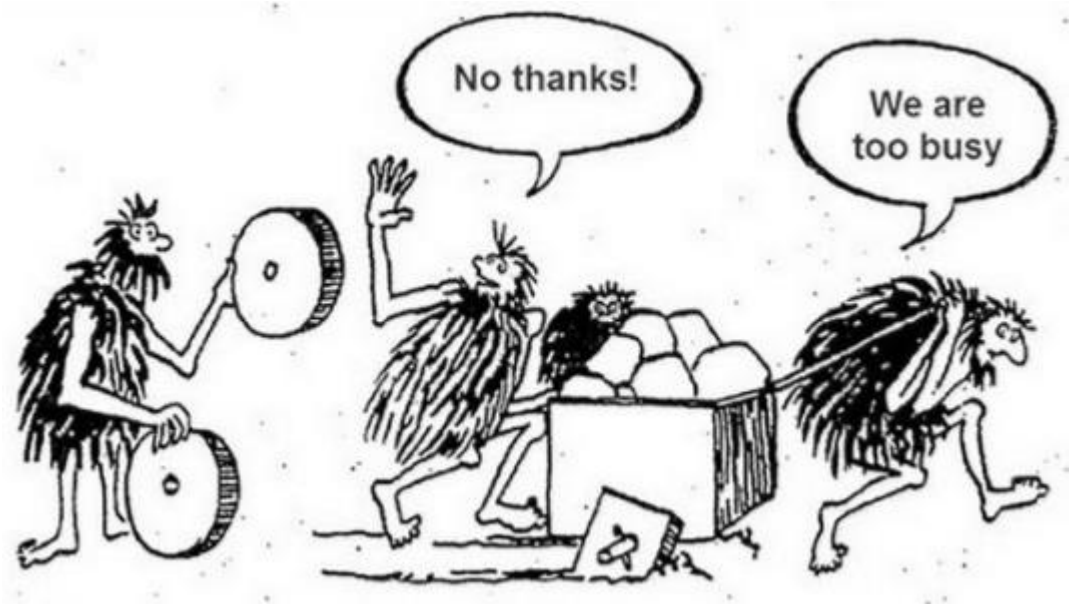

Figure 8: Investing resources into change will yield long term results (Kim 2015).

4.1.2 Regulatory Affairs – Roles & Responsibilities, and Potential for Lean

Belinda Jackson is the Regulatory Affairs Manager at Freudenberg Medical. With almost 25 years' experience in RA in the medical device industry, Ms. Jackson worked previously as a Global Regulatory Director in a company that sold Class III implantable devices globally. Having moved to Freudenberg Medical four years ago, Ms. Jackson is now the Regulatory Affairs Manager responsible for managing all RA tasks in the US site. Freudenberg Medical have comprehensive technical capabilities ranging from design and manufacture of minimally invasive, catheter, and handheld technologies (*Freudenberg Medical* 2017). Freudenberg Medical (FM) acquired Helix Medical and InHealth Technologies a few years ago. InHealth Technologies is the FM brand of ENT (Ear, Nose and Throat) products, such as voice prostheses and their accessories (*InHealth Technologies* 2017). The products are Class I and Class II in the US; Class I, IIa and IIb in Europe; and a mixture of Class 1, 2 and 3 in Canada. The ENT products are sold in US, EU, Canada, Australia, New Zealand as well as many other countries. The short-term goal is to have these products approved in Latin America and then long term, look at the Asian markets.

Faced with the challenge of expanding FMs market reach, Ms. Jackson understands the workload associated with bringing devices to new markets. When she joined FM, her RA group

was managing a lot of work that other groups should be involved in e.g. biocompatibility report generation. Although a lot of progress was made, there is still work to be done. When asked what the typical day to day workload involves in an RA role, it is quick to see that they are involved in a wide range of activities. Ms. Jackson would see regulatory submissions as the most enjoyable aspect of RA. "We enjoy product submissions and getting our products approved in new markets. That is what we strive to do as regulatory professionals". FM is working on several product registrations in new markets and there are also updates required to technical files for older devices. The Technical Files are standardised but the product submissions for other countries are not standardised. They require customization for each market. "For our EU Technical Files, follow our Notified Body guideline. It is a STED format but addresses their specific requirements. We follow that guideline to keep them happy. For other countries, we customise the product files". However, product registrations are only one aspect of the RA role. There is a lot of compliance work, related to Notified Body follow up or FDA follow up, which is necessary but can slow down other areas of work. RA is always involved in complaints handling, especially regarding reporting and vigilance. Other everyday tasks include but are not limited to include reviewing reports and documents for design files; design and development plans; biocompatibility documents; review of engineering change orders; review of validation; marketing documentation to ensure that a claim is substantiated and in compliance with submission; and clinical evaluation reports. Ms. Jackson would say that Clinical Evaluations Reports (CER) would be the most challenging of the tasks, especially ensuring that they are in line with the latest regulatory requirements. It is evident that the RA role is very diverse and reaches into most aspects of a company (Jackson 2017a). With such a large workload, it is important for the RA department to work efficiently and effectively. As "lean enterprise" is at the core of FM business, has Ms. Jackson seen this filter through to the RA department?

Lean principles are embedded into the everyday business practices of FM. FM adheres to a proprietary process called "Growtth®", which stands for "Get Rid of Waste Through Team Harmony" (*Freudenberg Medical - Growtth® Our Lean System* 2017). Ms. Jackson is familiar with lean tools and uses them in her every day work. An example of this is a business process kaizen that was completed for the Quality System processes, which included the complaints handling process, specifically focusing on time management. The kaizen team of twelve people was led by the Director of Quality and the Lean Manager, and included members of the quality and regulatory team. The kaizen began with a "Group Question". The group was asked how each of them determines what they should be working on every day. The group responded with eleven different answers. This helped to highlight how each person tends to be working on different projects with different goals, which can slow things down for the quality and regulatory group. The team then decided to work on their Quality Board, a visual management board, to provide a clear and uniform direction for the team. The Quality Board that was currently in place was not being used effectively and the layout had not been optimised (Figure 9). Using the 5 whys method, the team established that the board would be a useful tool, if there were rules in place determining what information would go on the board, and if the up-keep of the board did not involve too much work. The team brainstormed different ideas which fell into the categories of layout, meetings, process owners, priorities, ease of input and flow of the

board (Figure 10). In the end the team drastically simplified and streamlined the board. They also improved the structure of the meetings to update and review the board. The new layout meant the roles and responsibilities could be reviewed and defined by the group twice weekly. With the new Quality Board in place over six months now, Ms Jackson believes it has made a big difference in their time management. "Each complaint, CAPA *(corrective and preventative action),* and NCMR (*non-conforming material report)* is added to the board. The board shows the person responsible for the task in the group. There is a flow to the board. When something is higher priority, it is put in a certain bucket. It is very visual and helps the Quality Director see where everything is at" (Figure 11) (FreudenbergMedical 2017, Jackson 2017a).

Figure 9: the FM Quality Board prior to the Quality Time Management Kaizen Event (FreudenbergMedical 2017).

Figure 10: FM Brainstorming of different solutions to improve the board (FreudenbergMedical 2017).

Figure 11: The new FM Quality Board after the Quality Time Management Kaizen Event (FreudenbergMedical 2017).

Although this is a great example of how lean tools can be used to improve time management for QA/RA tasks, FM has not completed any kaizen events on any specific regulatory processes. When asked whether lean is suitable for regulatory process, Ms. Jackson thought it would be possible but it would be difficult. "It would be difficult to navigate through the grey areas. With lean processes, you have decision trees that work for all eventualities. For regulatory, you could develop some decision trees but there would be so many branches" (Jackson 2017a). Ms. Jackson would see lean tools to manage the increasing workload of the new regulations. "If everyone on the team agrees on priorities of the project, with compliance coming first then this is in line with the Growtth® philosophy of Freudenberg. Prioritising is Growtth®" (Jackson 2017a). When asked if she was concerned about how FM will manage with the transition to the new regulations, Ms. Jackson feels that they are ready and prepared for the work. They are fortunate to be able to hire new people if required. With almost 25 years' experience in RA, Ms. Jackson knows as a rule, regulations tend to get more complicated over time. Having dealt with countries that did not have regulations but now have adopted regulations, she sees they usually adopt similar regulations of similar structure to the EU. Although more complex and potentially a bit of an overkill, Ms Jackson does see a lot of good coming out of the new European regulations. Where previously there was not a level play with NBs, some NBs were looked on as easier to get CE Marking. "In the last few years there have been big improvements and there is more of a level playing field" (Jackson 2017a).

As a company with lean principles at the core of its business philosophy, Freudenberg Medical has the resources and experience required to really benefit from implementing lean regulatory processes. Even though Ms. Jackson understands that it would not be an easy task, she does see the potential of using lean tools in RA. Having seen first-hand the improvements that lean tools have made on the time management of CAPA, NCMRs and complaints, there are so many opportunities for improvement within the RA department. The RA department is involved in so many tasks, across many departments, there are many potential areas to complete business

process kaizens e.g. change control; design and development planning; medical device reporting and vigilance; and technical file compilation/updates. The use of visual management boards could be introduced to more of the RA functions, to help with accountability and traceability. There is so much variability in RA, as requirements depend on the device and the country it is marketed in. Where possible, processes should be standardized, as it will improve the quality of data and ensure consistency across all products and registrations. Any company with a strong lean philosophy is always moving through the cycle of continuous improvement. Freudenberg Medical is already using lean tools in all areas of the business, including areas that RA is involved in. In time, they will move onto lean projects, specifically focusing on the RA department. With so many regulatory changes happening now, it is likely that these projects will be initiated soon.

4.1.3 International Regulatory Affairs – Management Perspective

Tony Keaveney is the VP of Regulatory Affairs Europe and International at Merit Medical, a leading manufacturer of medical devices used in diagnostic and interventional cardiology and radiology procedures (*Merit Medical - About* 2017). Founded in 1987, the company has six design sites, 10 manufacturing sites and 12 distribution sites. It manufactures over 1300 products, with varying risk classifications over its five divisions of cardiac intervention, peripheral intervention, oncology and spine, endotherapeutics and OEM (*Merit Medical - About* 2017). Merit Medical has seen rapid growth outside of the EU and US in the past five years, so Mr. Keaveney understands the challenges of dealing with global regulatory affairs. He sees first-hand how global regulations are growing in complexity due to increased regulations, increasing enforcement and rising costs (Keaveney 2017a). When Mr. Keaveney joined Merit Medical, over 5 years ago, he was faced with several immediate challenges as the company was growing rapidly. He found that regions quickly became isolated due to focus on the larger, more established markets such as EU and US. This was not by intent, but just how the organisation was evolving. There was poor communication and poor flow of information. Mr. Keaveney says "We were expanding into other markets. The challenge was not just a regulatory challenge, it was a challenge across the entire organisation, be it sales or marketing. Almost all the functions that have an international element experience the same difficulty, and that is communication. Poor communication, poor flow of information, with everything being US and EU focused, and that primarily causes the difficulties".

The first step in overcoming these challenges, was de-centralisation of International RA responsibilities from the US out to the regions; EMEA, Asia, Central and South America. Having this regulatory presence in different countries gave Merit Medical the ability to respond much more quickly to local market needs, address local issues with local expertise and to increase local flexibility by taking direct ownership of product licences instead of them being owned by local distributors. The next step in overcoming the challenges of rapid growth, was to improve communication. With increased corporate leadership awareness, Merit Medical worked on bridging the gap between the sites and the regions, developing active partnerships between the RA teams and the regional sales. Merit Medical recognised that RA has a unique position with access to a broad breadth of information that most departments don't have access to. Regulatory Affairs is one of the few functions that are directly involved in both site activities

and projects, and regional sales activities. Understanding this unique position makes the RA function key in improving communication and project planning, but to make the most of this, Merit Medical needed to change the way they worked. They needed greater transparency, better data and in turn this would enable them to make better decisions. This is how the "ePathway" was developed (Keaveney 2017a).

As Merit Medical has vast experience in the US and EU markets, they developed comprehensive pathway documents that covered the strategies for these markets. It outlined classifications, market access routes, applicable standards etc. Although the pathway documents did address global requirements, there was a lot of information missing. Over the last four years, Merit Medical have been working on building their international data. "The intent of the pathway document was to provide feedback on the process changes to the site teams, be it R&D or a manufacturing team. This would allow the team to plan the change by assessing the global impact. So, when the team are initiating a change, they know it may only be a Special 510(k) in the US, with 40-50 days' review time; but the same change is going to take 18 months in China. That was invisible in the process before. Now the team have this information to hand and now they can work on how they can bridge that gap. They are many ways in which engineering can respond and manage that delay. But the important thing was, is they were getting information in a way that they had never had before. That's how the pathway process started"(Keaveney 2017b). It was at this point that Mr. Keaveney looked at how they could make better use of technology. "We have all of these platforms used every day, socially to connect each other. We have live flow of information in every other aspect of day to day living, yet here we were with a 16 or 17-page document that was growing and becoming increasingly difficult to deal with. So, we looked at electronic platforms that could serve us". Working with their IT department, they developed the ePathway as a web based RA assessment and reporting tool. It allows for greater transparency, improved flow of data and better decisions. Prior to a site initiating a change, the RA Specialist at that site will enter the details of the change and the applicable regions into ePathway. The RA Specialists in the applicable regions will get automatically notified of the change. They will assess the impact of the change and determine if there is a pre-notification requirement, pre-approval, or any unique requirements. When they complete their assessment, the information is saved to the system. The RA specialist at the site of origin can check the status of the assessment. One of the long-term plans for the system is for it to automatically generate a Gantt-like view of the change timeline, based on the feedback from the various sites. The software takes a lot of the inefficiencies out of the process e.g. automatic email notifications of progress.

In the early days of developing the software, Merit Medical could see the potential for developing platforms to improve communication and visual management of a project. Using a software platform called DOMO, they could take data that is in any format e.g. excel or oracle, and filter it into graphical representations of the data the user needs. Using this as the visual front end of the platform, these DOMO cards give the stakeholders overviews of the process. Within a few clicks, someone from management, sales or R&D can login via their phone, iPad or browser, and filter down to a particular pathway. They can immediately see the status of the implementation of that change, in terms of the plan and where it is along the process. Just as a

manufacturing lines use tier 1 and tier 2 huddle boards, these DOMO cards are equivalent visual management tools for International RA. "Data should highlight delays, inefficiencies and difficulties within the system. Those bottlenecks in turn, just as in manufacturing, will be the basis for the discussion on how can we improve that particular part of the process; how can we refine it; how can we remove those bottlenecks and identify performance issues/ areas of low performance" (Keaveney 2017b).

Although this new system is not fully implemented across all sites, there was positive feedback on ePathway. The 3-month pilot program was completed and they intend to make changes and improvements to remove inefficiencies that were not apparent at the design phase. Merit Medical intend to have the ePathway fully replace the paper system within the next three months. It is important for them to drive the implementation of the platform as they know it will benefit the business. It can help them better understand global trends both internally within the company and externally with the international regulators. This will improve communication with the different functions; improve the quality of future data; reduce the questions between sites and regulators; and reduce the time to market. Mr. Keaveney sees first-hand how the regulatory environment is increasing in complexity. There are increasing workloads and increasing demand for more detailed information. However, he recognises that it is not feasible to just keep adding resources and sees the need to innovate rapidly as key to have sustained performance improvements (Keaveney 2017a). Merit Medical are focusing on how their organisation can work more efficiently and effectively in the complex regulatory environment. Mr. Keaveney was asked for his opinion on what regulators should be doing to adapt and manage the constantly evolving industry. He agrees that regulations are becoming more complex and the time to market is increasing. However, he finds it hard to argue with most of the changes. The key to developing regulations, is to remain flexible. Taking the EU as an example, the MDR seems have taken a reasonable approach with this, but there is still a lot of ambiguity in terms of how the regulations are going to be implemented. "In summary, there are three things to consider with regulations. It is about ensuring that the regulations are flexible in the first part; that the regulators are pragmatic in their interpretation in the second part; and that manufacturers are conscientious in third part" (Keaveney 2017b).

Although Merit Medical have not used lean tools for their regulatory processes, Mr. Keaveney does see them progressing to a more typical lean approach. "We have a long way to go to be in the same field as Shingo award winners, that is where the long term goal is" (Keaveney 2017b). Merit Medical know that if they are to maintain their rapid growth in a sustainable way, they must adapt and innovate rapidly. Although they have not specifically used lean tools, they have adopted lean principles. With the implementation of the ePathway, Merit Medical have eliminated many forms of waste that were in the process. The worst form of waste in a business process is over-information as it is a hidden waste that leads to all other types of waste. Merit Medical have cut a lot of over-information in their process, as previously the international regulatory requirements were not clearly defined; there was a lot of emails going back and forth between sites and departments; potential duplication of work; and potentially unnecessary meetings to agree on regulatory strategies. Process waste was eliminated through standardisation and reducing the lead time in gathering the necessary information. The amount

of rework should be reduced as there are clearer guidelines and instructions for personnel. People are less likely to make a wrong decision or give incorrect information. The use of software to trend data will also allow for better understanding of regulatory requirement and reasons for submission rejections or follow up questions. This in turn will remove the need for follow up due to poor quality of information. The waste of searching and waiting was reduced as the information required is now in one central location and the use of visual management boards mean that relevant stakeholders can quickly get summaries of project status. The transfer of information was simplified as the information goes directly to the relevant people. Visual Management is another component of lean manufacturing that Merit Medical have implemented. Using visual management tools for regulatory processes provides transparency and allows management and team members to rapidly discern the impact of any details on the on project or business. After all, accountability and transparency are essential to a successful market access strategy. Even though the ePathway was initially developed as a web-based RA assessment and reporting tool, there is a lot of potential to expand this even further throughout the different RA functions and the wider organisation. Merit Medical recognise the unique position that RA has within a business and are using this to their advantage to enable sustainable growth within the business. They are a great example of how companies need to innovate and change the way they work to meet challenges of working in the medical device industry.

4.1.4 International Regulatory Affairs – Consultant Perspective

Benjamin Arazy is the President and CEO of Arazy Group Consultant Inc, a regulatory consultancy company that assists medical device manufacturers with regulatory submissions as they enter new markets. With over 20 years' experience, Arazy Group operates in over 100 countries worldwide, serving early start-up, medium sized, and multinational companies (*Arazy Group* 2017). Arazy Group started as small company dealing mostly with US and EU market access for the first 10 years. During this time, Mr. Arazy was looking at the resources the company had and the processes they were engaging in. He realised there was a lot of redundancies and repetition in the processes due the manual nature of the work. "Because of the human factor involved in the review process we will never be able to eliminate 100% of non-conformities." At the same time, there was also a change in the market because of the recession caused by the financial crisis of 2008. Arazy Group were getting a lot more enquiries from US companies wanting to ship products outside of the US to compensate for loss of business due to the financial crisis. Arazy Group could not expand their business to manage more than just US FDA and CE Marking in an effective manor, unless there was a better tool to manage all the complexities. This is where the idea for Licensale started.

To create this new "tool" to manage these varying regulatory requirements, Mr. Arazy went back to the basics of regulatory affairs. "Ultimately, a device is a device, regardless of the country it is sold in. A pacemaker is always a pacemaker; an ultrasound is always an ultrasound, regardless of it being sold in Kazakhstan or Australia. When you look at the risk model, the risk to the patient is always the same." Although Mr. Arazy does acknowledges that there are global harmonization efforts happening, he does not believe that it will get to a place where medical devices can be shipped freely between countries, as there are other factors that come into play.

"Apart from the human factor, it is also about political power and money. Countries are not going to give away their ability to charge for their process". So instead of waiting for harmonization, Mr. Arazy decided to focus on what he could do with the current system. When comparing the medical device industry to other competitive industries such as the electronics and computer industry, while they use different technologies, they agree on the tool or format e.g. USB cable connectors. "Harmonization is about agreeing on the standard and agreeing on the tool". This is the same principle for Licensale, as it is a new tool for regulatory harmonization. Having worked in manufacturing in his early career, Mr. Arazy is familiar with *Just in Time* concepts. "The challenge has not changed. How do you do the most, with the least effort? Now we are just using a different tool". Just like lean tools, this regulatory tool is about "the management of data and knowledge"

Figure 12: Licensale is a system that allows alignment of business strategy and regulatory strategy to allow growth (ArazyGroup 2017).

When it came to developing this new regulatory tool, there was a lot to consider. There are so many similar and vertical problems across all devices and regulatory submission requirement. Arazy Group had to develop a software that could manage data and information, and recognize patterns and repetitions. In simple terms, Mr. Arazy looks on regulatory affairs as a combination of data and knowledge. "It is the collection of compliance information to prove the safety and efficacy of a product, so basically it is the management of data". However, Licensale not just successful because it is an automated software tool that can manage the complexities of

thousands of variants of devices across over 100 countries. It is also an "expert system", which takes the human factors into consideration. The aim is not just to deliver applications in quickly, but to deliver successful application. Behind every Licensale application is a series of regulatory experts reviewing the documents to ensure compliance to the relevant regulatory and device requirements. Arazy Group have termed this as "knowledge above the cloud".

Although the cloud-based software application has had great success in the four years since it was implemented, it has not been without its challenges. Like the challenges with implementing lean principles in a workplace, people's resistance to change was one of the big challenges for Arazy Group. Very little has changed in regulatory affairs in the past 40 years. "It remains a fragmented, costly, and inefficient process, managed manually and mostly through distributors and consultants" (*Arazy Group* 2017). Even though most Regulatory professionals are aware of these inefficiencies, there is still hesitation to change. When asked how Arazy Group overcame this challenge, Mr. Arazy said education is key. There are a couple of stages to Arazy Group's education process. The concept of Licensale was first developed as an internal tool. It was used internally for a couple of years to overcome the challenges that they knew existed. Arazy Group understands the challenges that the customer will face when starting to use Licensale. This is the first step in the education process. "With 20 years' experience, Arazy Group understand the regulatory business so well that we developed a tool to provide the solutions we needed and our customers needed". The second stage in the education process, is to train the customer on how to use Licensale. All customers receive an hour training session and generally start off with one project, to get their head around the change. A large percentage of Arazy Group's annual work is repeat business. Mr. Arazy says "if the customer has a positive experience with the portal, they won't go back to their old way of working. It is like going to from an iPhone back to a dial phone".

There are other challenges that Arazy Group face with the Licensale. Gaining the trust of manufacturers is one. The future of a manufacturer does not only depend on their ability to innovate; it also depends on their ability to get their products to market. A medical device is only valuable when it is available on the market. There are a lot of decision maker involved in this process. It is critical to get these key stakeholders on board to understand the benefits of using this system; having one contract and one central location for everything. In Mr. Arazy's opinion "it would be easier to sell a simple document control system, than a complex system like Licensale, as it is going to be the make or break of the company growing over the next few years and getting their product onto the market". There is also the issue cost. Customers will challenge costs, especially when there may appear to be a cheaper solution out there. Arazy Group may require more of an upfront investment when compared with other distributors or consultants. However, working with distributors or consultants require more money and time to be invested throughout the entire regulatory process. This is where Licensale's unique selling point comes into play. Arazy claim they can reduce time to market and costs by up to 50%, when compared with other solutions. This is the aim of any lean tool, to reduce cycle time and reduce costs. For further details on how Licensale works and its effectiveness, refer to section 4.3 of this chapter for the Licensale Case Study.

4.2 VistaMed Case Study

4.2.1 VistaMed & Lean Systems

VistaMed is a leading provider of complex extrusions, finished catheters and devices to the minimally invasive medical device industry, specialising in providing design and manufacturing expertise from concept development to finished product (*VistaMed - Innovative Catheter Solutions* 2017). VistaMed were partnered with the global medical device and healthcare manufacturer Freudenberg Medical in 2010. Freudenberg Medical have capabilities in product design and development, silicon/thermoplastic moulding, thermos plastic extrusion, hypo-tubing, device assembly and packaging across its eleven manufacturing sites worldwide (*VistaMed - About Us* 2017). It is through this partnership with Freudenberg Medical that VistaMed have been able to expand its lean capabilities. Lean principles are at the core of every business practice across all of Freudenberg Medical (FM) facilities worldwide. Freudenberg are used as an example of the application of the one of the five lean principles in 1996 Womack and Jones' book Lean Thinking (Chapter 5 Womack and Jones 1996). Freudenberg has developed a proprietary process called "GROWTTH®", which stands for "Get Rid of Waster Through Team Harmony". Its aims to eliminate waste, optimize value-added activities and reduce lead time throughout the processes, using lean tools such as Kaizen, Value Stream Mapping and 3P. As a program that is in place for 30 years, its philosophy permeates through all areas of the organisation, from device concept, right through to a finished product being shipped out the door. By applying GROWTTH® tools, VistaMed and FM are able to systematically identify waste and streamline processes, regardless of whether the process is run in production, in the cleanroom, in the warehouse, or in the office (*Freudenberg Medical - Growtth® Our Lean System* 2017). Some of the lean tools used in GROWTTH® are kaizen, value stream mapping, and 5S. While these tools are most commonly used on the manufacturing floor, there are many other supporting processes that they can be applied to. Business processes that are close the manufacturing process include scheduling, incoming inspection, receiving, purchasing, and shipping. Then, there are the wider processes such as product development, customer returns, payroll, accounts payable, supplier development and accounts receivable. All of these processes have waste. This case study will look at how VistaMed have applied lean tools to eliminate waste, optimize value-added activities and reduce lead time in some business processes. It will assess the suitability of these lean tools to eliminate waste, optimize value-added activities and reduce lead time in regulatory processes.

4.2.2 Business Process Kaizen – Raw Material Specifications (RMS)

4.2.2.1 Background

In VistaMed, there are monthly operations review meetings. One of the aims of these meetings is to review each area's KPIs (Key Performance Indicators), and identify areas for improvement within each department. The R&D department in VistaMed manage all new design and development projects for VistaMed's customers. To stay competitive in the industry, VistaMed must be able to commit to quick timelines, while not compromising on quality and compliance. This is one of the reasons a large volume of VistaMed new projects come from repeat business.

One of the key performance indicators (KPIs) for the R&D department is project timeline. It was identified in a monthly operations review meeting that some projects were not meeting their monthly timeline target dates. An investigation was completed and it was established that the process for ordering materials was slowing down the project. Specifically, the timeframe from when a customer Purchase Order (PO) is acknowledged, to when a supplier receives the PO for the raw material components. As a contract manufacturer of minimally invasive devices, VistaMed specialises in catheters based platforms used in diagnostic and therapeutic procedures or combination devices (*VistaMed - About Us* 2017). VistaMed does not offer off-the-shelf products. Each device is designed and developed based on specific customer needs. These are high specification devices, manufactured to very tight tolerances. Therefore, each device needs customized orders for special components materials. Receiving materials is the longest lead time in the entire project lifecycle. Therefore, placing orders for materials as soon as possible is critical to keep the project timeline on track. One of the main ways VistaMed stays competitive and avoid project delays that are out of their control, is to bring as much of process as possible in house e.g. extrusion, moulding, braiding, coiling and 3-d printing. However, there are always specialised materials VistaMed must order. Some of the longer lead time items include medical grade resins, high tolerance stainless steel mandrels and radiopaque marker bands. When a PO is received from a customer, VistaMed aim to have all materials ordered within six working days. This six-day period is dependent on a lot of steps moving forward quickly. When project timelines were reviewed, it was established that this process was not happening in six days. For some projects, it was taking as long as 15 working days. To improve these timelines, it was decided to complete a business process kaizen on the raw material specification (RMS) process to improve the process and reduce the lead time.

4.2.2.2 The Kaizen Event

As discussed in the interview with the Lean GROWTTH® Manager, the key to a successful kaizen is to plan it properly, allow sufficient time and include the correct people. The facilitators of the event were the Lean GROWTTH® Manager and the Senior R&D Engineer. The other team members include the Operations Manager, the Quality Manager, the Supply Chain Co-ordinator and the R&D Engineer Assistant. The team included decision makers and people that were involved in the process every day. The agenda and pace were set for the event. The first item on the agenda were introductions and training on the GROWTTH® Lean Administration Manual. The next step in the process is to map out the current state of the process

4.2.2.3 The Current State

There are many different steps within the process. In the lead up to kaizen event, several RMS were tracked through the process the establish the current state. Refer to Table 4 for a summary of current process. The team completed the handover analysis of the current state process, with swim lane analysis to track the handovers (Figure 13). It was established that there were 28 handovers per RMS. Handovers are a source of waste, so the aim of the Kaizen was to reduce the number of handovers.

Table 4: Current Process		
Step	*Details*	*Best Case Time (Days*
1.	Acknowledge customer PO	-
2.	Draft raw material specification (RMS)	0.5
3.	Obtain quotes initial confirmation from vendor that they can commit to the specification	2
4.	Initiate an Engineering Change Request (ECR) - Required to generate the RMS document, that outlines the components specifications.	0.5
5.	Approve ECR	2
6.	Review and approve RMS	2
7.	Send RMS to vendor to sign	2
8.	Place Purchase Order with Vendor	-
	Total Time:	9

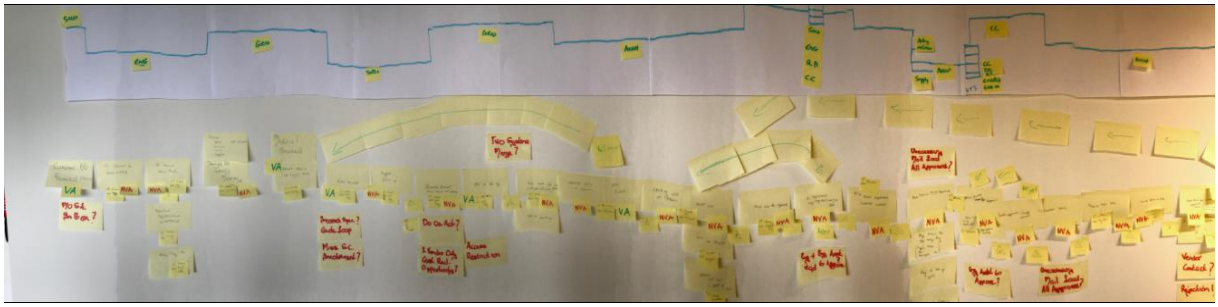

Figure 13: Current state map with handover analysis on the top row.

4.2.2.4 Value Added and Non-value added analysis

Before optimizing the process, each step was reviewed to identify the value added (VA) and non-value added (NVA) steps. It was determined that the VA time in the process was 47 minutes and the NVA was 11,146 minutes. Therefore, the percentage VA time was 0.4%. Typically, a process is 1% value-added. A root cause investigation of why there is so little VA time is required to really improve the process. If the root causes are identified, it becomes easier to generate the future state map. The root cause investigation showed that the document approval process accounted for 97% of the process. There was a large amount of approvals, as people had to approve the ECR and RMS, and in practice, the approvals were being completed in sequence, not in parallel.

4.2.2.5 Regulatory Requirements

At a minimum, the future state map must comply with the applicable regulations and it must consider the limitations of the QMS and ERP systems. In this case, the applicable regulations were ISO 13485:2016 and 21 CFR Part 820. To meet the minimum requirements for purchasing product, the purchasing information should include the product description; the specifications; the requirements for product acceptance, including procedures, processes, and equipment. There must be a written agreement in place that the supplier must notify the manufacturer of any changes that may impact on the purchased product specifications (Part 820 *Title 21 CFR* 2016, *ISO 13485* 2016). The VistaMed Purchasing and Vendor Management procedures and

Raw Material Specifications addressed these requirements. There is a requirement to have a documented process for evaluation, selection and monitoring of suppliers and the controls must proportionate to the risk of medical device they are used in. Therefore, VistaMed Vendor Management procedure states a supplier must be on the Approved Vendor List (AVL) and must be assigned a rating, based on risk of the purchased component. Adding a new vendor to the AVL or changing the risk level of a vendor, is considered a change to the QMS. The manufacturer is required to ensure the integrity of the QMS is maintained when planning and implementing changes to the QMS (*ISO 13485* 2016). Therefore, the current process in VistaMed, required that any new components that VistaMed purchased required an ECR, so consider the impact on AVL.

4.2.2.6 Map out future state

Before mapping out the future state, a brainstorming session was completed using the lateral thinking technique. Lateral thinking is defined as "the solving of problems by an indirect and creative approach, typically through viewing the problem in a new and unusual light" (Stevenson 2010). Using this quick-fire thinking technique, over 60 ideas were generated. However, it is not realistic that the best and simplest idea can be taken forward for the future state map. The root cause investigation highlighted the inefficiency of using the ECR process to approve new RMS. As part of the brainstorming session, a suggestion was made to replace the ECR with a simpler one page assessment. There would a weekly/daily meeting with the appropriate personnel e.g. Project Engineer and QA/RA Engineer, and they would complete the Assessment document. The Assessment would start by asking if the vendor was on the AVL or if the vendor rating was impacted. If any of the questions were answered "yes", an ECR was required. If both were answered "no" the Assessment document would be complete, the RMS would be loaded to the Doc Control system and the appropriate personnel would review and approve the RMS at that time. The best-case scenario for the current process was 9 days to complete. The main goal of the Kaizen event was to reduce the number of handovers in the process. With the future process (Table 5), the time to complete was reduced by 44% to 5 days.

Table 5: Future Process

Step	*Details*	*Best Case Time (Days*
1.	Acknowledge customer PO	-
2.	Draft raw material specification (RMS)	0.5
3.	Obtain quotes initial confirmation from vendor that they can commit to the specification	2
4.	RMS Assessment and Approval meeting	0.5
5.	Send RMS to vendor to sign	2
6.	Place Purchase Order with Vendor	-
	Total Time:	5

4.2.2.7 New process lead time/kaizen success

At the end of the Kaizen event, the Assessment document was drafted by representatives from Engineering, Supply Chain, and Quality. The quality procedures were red-lined to detail the

new process. The ECR to implement the changes was also drafted. On completion of the Kaizen, the summary of the event and outcomes were presented to the wider team. An action list was put in place. Action items included the completion of the change request; the training on the new process; setting up weekly/daily RMS Assessment meetings; and implementation of visual boards to track the lead times on the process.

Although this Kaizen was not an RA Kaizen, it demonstrates how Kaizens can be used for compliance processes. It outlines how to structure a Kaizen; how to assess the current state through handover analysis, and VA/NVA analysis; how to map out the future state, with particular focus on the regulatory requirements; and how to implement the actions effectively. The exact same principles would apply to regulatory processes. Although it may seem like the hard work is done when the Kaizen event is over, the actual hard work is in implementing and maintaining the new standard. Regardless of whether the process is on the production line, or on a business process, the challenge is always the same. If Kaizen is used to improve an RA process, the implementation of visual boards will help maintain the effectiveness of the new system and would also highlight areas for future improvements.

4.2.3 New Product Introduction – Standard Process

VistaMed develop a wide range of catheters including neurovascular, intracranial, vascular/venous access, electrophysiology & RF ablation catheters, percutaneous drainage, endoscopic, peripheral stent systems, vertebroplasty systems, epidural & pain management systems, drug eluting stents and aortic valve replacement. With such a wide variety of product, no project is the same. To ensure that projects are handled in a timely manner, to a high quality and within budget, it is important to standardise the process, where possible. Although the products may be different, the project management approach can be standardised and the process for developing the products can be standardised. With lean thinking in mind, VistaMed have developed several ways to standardise the product development process, allow their customer to bring new devices to the market in a timely manner.

4.2.3.1 Project Management Stage Gate

Over the past few years, VistaMed's customers are coming to them with more complex, high-risk devices and are more often requiring VistaMed to take on more responsibility in the product lifecycle. This includes the management of biocompatibility testing, packaging validations, aging and transportation studies, finished product packaging and labelling, and sterilization. Therefore, the product development lifecycle is becoming more complex. To ensure that there is the correct expertise at each stage of the product the development, the organisation was split into three areas: R&D to focus on product development, NPI (New Product Introduction) to focus on process development and process validation; and Production. Design for manufacturing is at the forefront of all decisions, therefore input from representatives of each of the three areas are required throughout the process. The project management approach needed to be standardized to ensure that key items were discussed at critical stages in the project. The Project Gating Process was developed to address this.

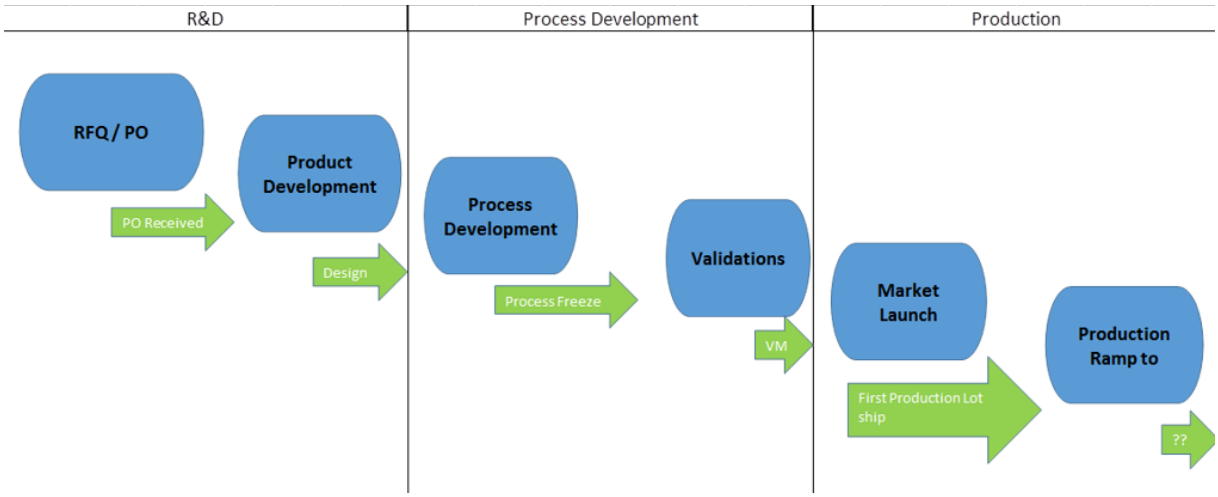

Figure 14: Project Gating process (VistaMed 2017)

The project gating process is divided into six key stages (Figure 14). At the end of each stage, the project moves forward when all critical items have been addressed.

1. Project Initiation Stage (R&D Team) – This stage begins with the customer issuing the new Purchase Order. At this stage, agreements are put in place, such as Non-Disclosure Agreements and Design Services agreements. User requirements of the device are addressed. Project Timeline is initiated, including assigning team members and responsibilities (Figure 15).
2. Product Design and Development (R&D Team) – This stage ends when the product reaches Design Freeze. The Design History File (DHF) must be up to date, as much as possible, and meet the regulatory requirement. Other requirements include packaging design and documentation. There must be initial releases of Process FMEA, Device Master Record and Validation Master Plans. Design Verification and Validation (V&V) Test Plan must be approved. The Project Timeline must address the Sterilization, Biocompatibility, Aging, and Clinical Evaluation, if applicable to scope of the project.
3. Process Development (NPI Team) – During this phase the manufacturing process will be optimized. Design V&V testing will be executed and Design Review completed. Sterilization Validation, Packaging Validations, Aging Studies, Biocompatibility and Clinical Evaluation will be underway.
4. Process Validations (NPI Team) – This stage will be initiated when process was optimized and process validations start. The DHF is completed included all of the Design V&V testing. This is the final stage before the customer applies for market approval in their chosen market.
5. Market Launch (Production Team) – The process validation has been successfully completed and customer have received their pre-market approval. As part of the initiation of this stage, all design transfer items must be closed out.
6. Production Ramp up (Production Team) – As customer launch their products in additional markets, the production volumes will be ramped up. The NPI team co-ordinate with Production to optimize yields and efficiencies.

Stage 1 Checklist - Project Initiation

Project Heading					
Current Status			R&D Planning & Specification		
Responsibility	Code	Design	Assessment Specific Criteria Requirements & Evidence	Planning Status	Status
					Acceptable
Stage 1	Input Req	PO Recevied			Unacceptable
					Exception Approved
Customer Service	C1 - A	Non-Disclosure Agreement in place		Acceptable	
	C1 - B	Request for Quote Questionnaire complete			
	C1 - C	Concept or Drawing available			
	C1 - D	Credit Check			
Project Rep.	C1 - E	Worksheet			
	C1 - F	Quote Letter			
	C1 - G	Design Services agreement		Exception Approved	
	C1 - H	PO Recevied			
	C1 - I	Project Gantt Chart draft with Team Members & Responsibilities			
Quality Rep.	C1 - J	Quality Systems Responsibilities Matrix			
	C1 - K	Quality Agreement		Exception Approved	
	C1 - H	Customer Spec (User Needs / Design Input)			
Stage 1	Output	PO Can be Acknowledged			
		Completed By.			
		Accepted By.			

Figure 15: Stage 1 Checklist (VistaMed 2017).

As a contract manufacturer, project scope can vary all the time, depending if it is a product transfer, or a new product design, or a new iteration of a product. Some customers require VistaMed to complete limited product V&V testing. Depending on the scope, some sections will be not applicable, so the checklist may be very simple or it may be very long and detailed. Regardless, there will be consistency in the approach. Mapping out the process with the stage gates and checklists make the process more visible and it will make it easier to see problems within the process. ISO 13485:2016 and 21 CFR 820 both require a documented evidence of design transfer to production. The Project Management Stage Gate process is a good example of how the regulations can be used to create lean processes and drive improvements and compliance.

4.2.3.2 5S – Standard Project Folder Layout

During the R&D phase and most of the NPI phase, all projects are managed in the Project Folders on the shared network. All documentation is managed and controlled at alpha revision. Prior to initiating process validations, documentation is transferred to the electronic document control system and moved to numeric revision. Using the Project Folder structure, there is a human factor involved, as there are limited electronic controls on documentation and therefore increased opportunities for error. For the process to run efficiently, the project folders must have a standard layout. Using the 5S method of organise the folders, has helped standardised project management and reduce the opportunities for error. Previously there was no structure but now anyone can go into any project folder and find the documentation they are looking for because all projects folders follow the standardised folder layout. The folder layout follows a typical Design History File layout, so it can be used by VistaMed or the customer for their regulatory submissions if required. The 5S project was completed as follows:

1. Sort – All documents in the folders were reviewed. Anything not applicable was either moved or deleted.
2. Set – The folder was organised into a set structure. This avoids searching for documents, as everything is clearly marked and organised.
3. Shine – Keep the folders clean and tidy

4. Standardize – the new format was proceduralised and all relevant employees are trained on how to manage and maintain the folders
5. Sustain – folders are reviewed as part of internal process audits to ensure standard is maintain. Folders are scored based on compliance to the structure. If a folder score is below a certain score a Non-conformance or CAPA may be raised, depending on the severity i.e. a Non-conformance is raised if the documentation is there but not in the correct location; and a CAPA is raised if critical documentation is missing from the folder.

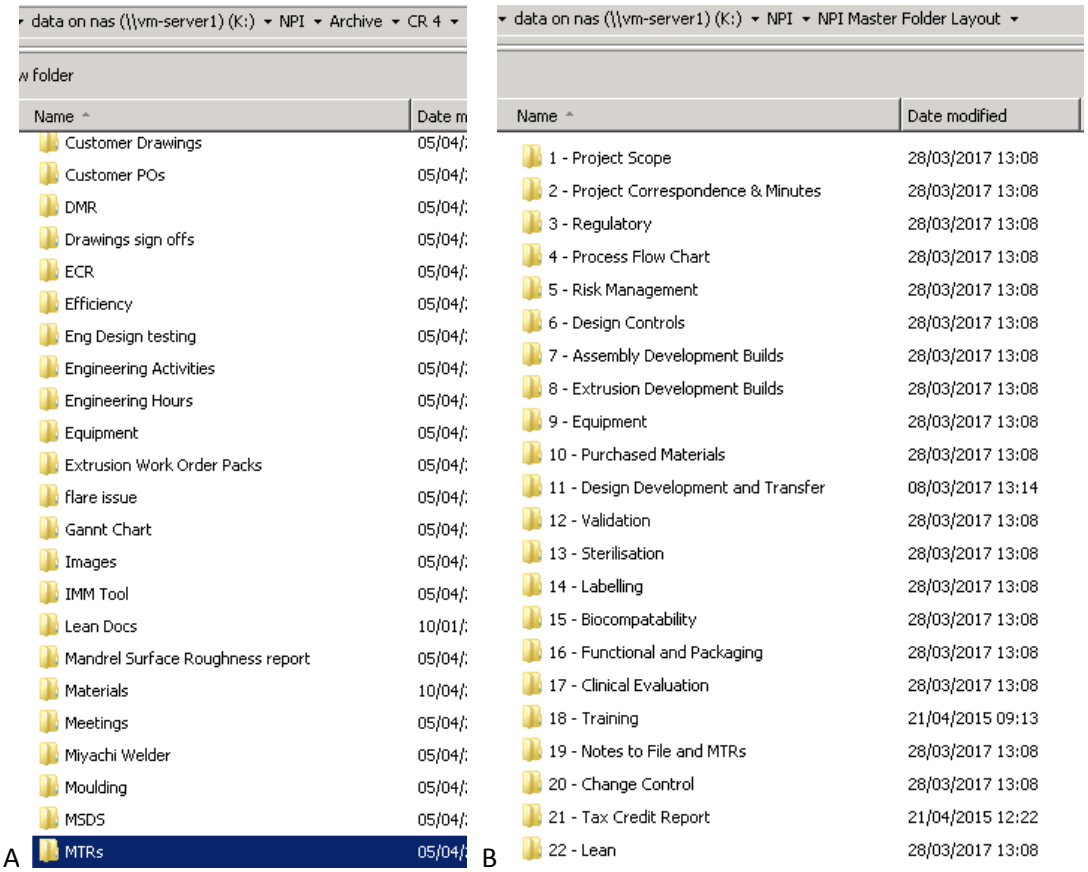

Figure 16: Examples of folder before (A) and after (B) 5S was completed (VistaMed 2017).

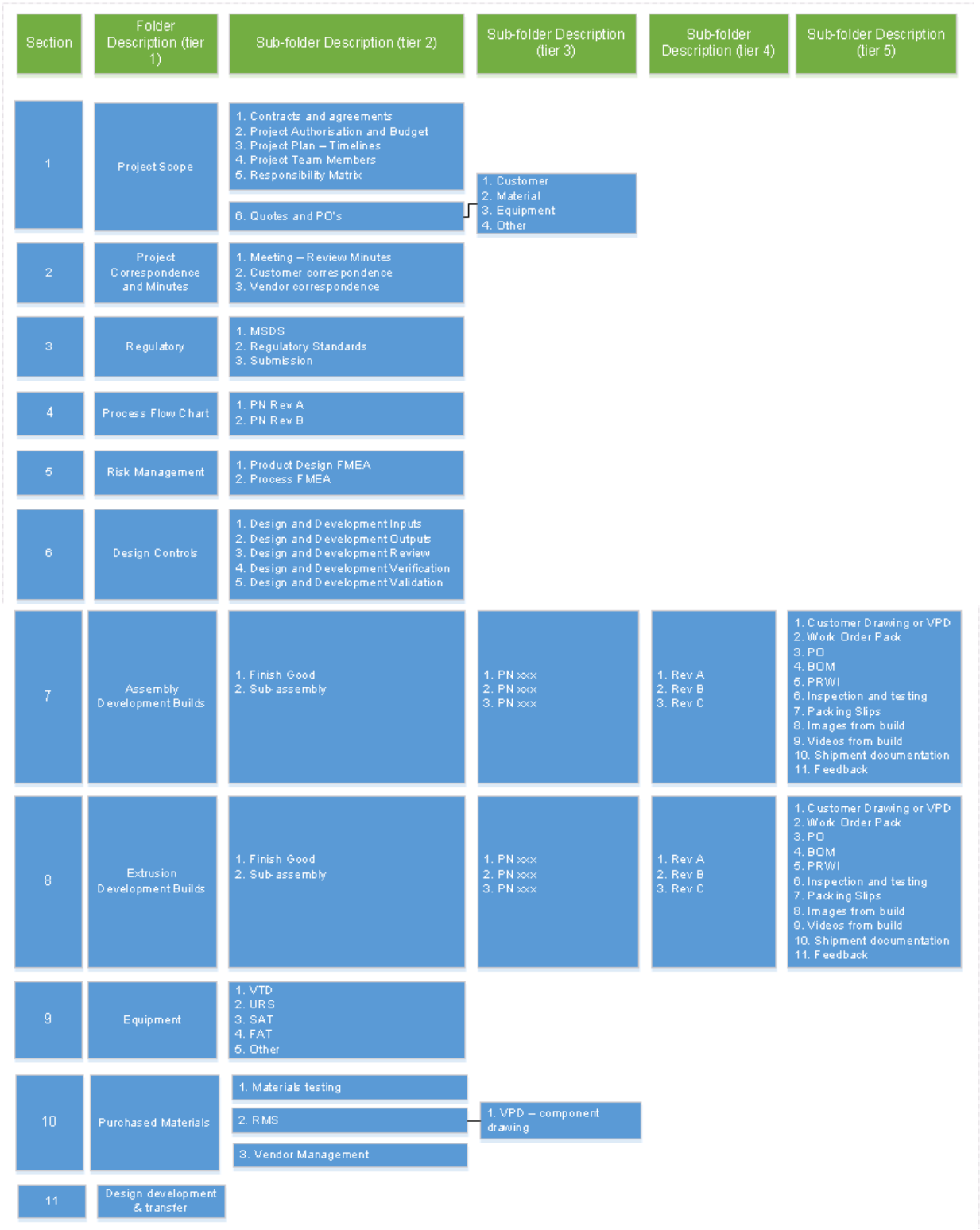

Figure 17(a) New folder structure including the sub-folder details (VistaMed 2017).

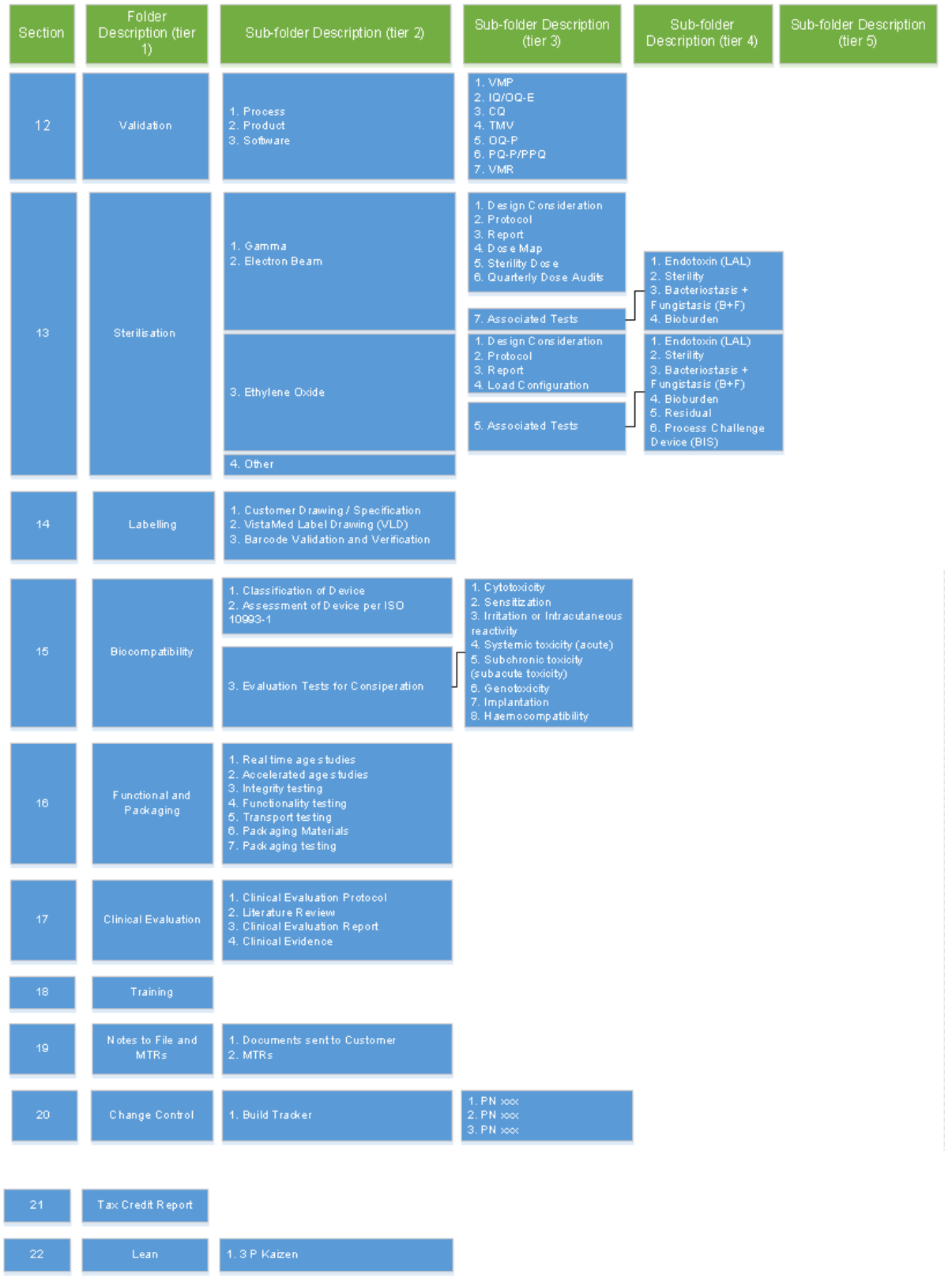

Figure 17(b) New Folder structure including the sub-folder details (VistaMed 2017).

The project folder layout has improved compliance to the New Product Introduction procedure and the Design and Development Procedure. The process was implemented since January 2015. A review of compliance to folder structure was completed recently. The audit reviewed 64

project folders, 14 were scored 100%, 48 were scored between 91% and 99%, and 2 of the projects were non-conforming coming in below 90% but greater than 81% (Figure 18). With only 2 out of 64 non-conforming, as success rate of 97%, shows that the process is effective. Having the structure in place is a prompt for the project to create the relevant documentation during the project stages. With all folders following the same standardised format, it makes project transfers easier. It also benefits the customer, as the format follows a DHF format, meaning they can use the folder for their regulatory submissions if required.

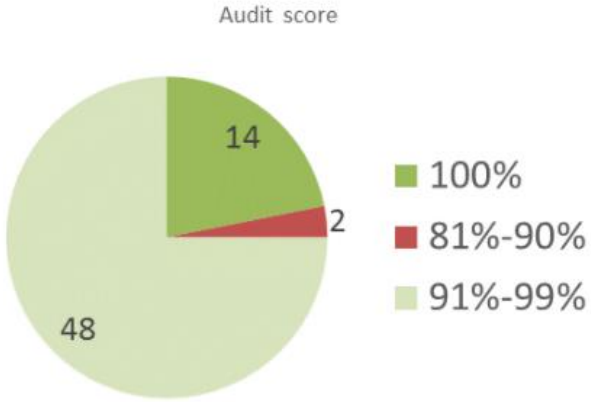

Figure 18: Audit of 64 Project folders (VistaMed 2017)

4.2.4 Summary VistaMed Case Study

VistaMed is not a legal manufacturer of medical devices, so it is limited exposure to certain RA processes e.g. Post Market Surveillance and Clinical Evaluation. However, RA has a cross over into many processes within the company. These examples show how VistaMed use the regulations when implementing lean processes. They show how VistaMed have effectively used Lean Tools to improve their compliance to processes. The examples above are ways that VistaMed have used lean tools to bring a product through development. It is only a taster of the potential for lean in speeding up the product development lifecycle, allowing their customers to bring their devices to the market quicker.

4.3 Licensale Case Study

4.3.1 Overview of Licensale

Licensale is an online customized Software as a Service (SaaS) developed by Arazy Group. It is a cloud based application, integrated with a network of regulatory experts, to optimize, plan, control and resource the entire regulatory life-cycle of a product (*Licensale* 2017). Arazy Group have combined the power of raw data, the efficiency of data management, and the connectivity of a professional social network into a new technology service platform and launched an integrated suite of cloud-based products designed to streamline, simplify, and expedite international regulatory affairs (*Arazy Group* 2017). Arazy Group have used this innovative platform to change their clients global licensing and registration processes, since late 2012. Arazy Group estimate that they can reduce both the time-to-market and license acquisition costs for their clients by up to 50%. This case study will compare the Licensale process with the

standard product registration lifecycle and establish if other medical device companies can adapt similar thinking to make improvements in their own processes, using lean tools.

Firstly, to understand how Licensale can save a medical device company up to 50% of time and money associated with bringing a device to market, we need to understand how it works. Arazy Group have termed Licensale as "Knowledge Above the Cloud™". This is because Licensale is not only a tool to manage product registration, it is also network of professional experts that review each document in an application to ensure that it complies with the relevant regulatory requirements. With this cloud-based application, Licensale not only impacts on how the Regulatory Affairs team functions but also other departments (*Arazy Group - Our Company* 2017):

- The legal department retains control of intellectual property, as they no longer need to work through distributers;
- The sales department is released from their dependency on local distributors, as the distributor is no longer the owner of the product licence;
- The business development department, can gain access to any potential new market in advance without the need for any prior presence or investment, as Arazy Group can gain access to over 100 markets world-wide.
- The RA department can become active partners of the sales and marketing, with control of the registration process in all markets throughout the entire product lifecycle;
- Entrepreneurs of start-up companies can create significant value just by having product compliance profiles in the system, making products accessible to any market within 3-12 months;
- Top executive's concerns are reduced as resources can be allocated and managed more effectively; and ultimately, all of this translates into growth, revenue, market share, profit margins, and stakeholder interest.

Licensale is built around GRIMS™, the Global Regulatory Intelligence Management System. GRIMS™. It provides regulatory intelligence relating to registration requirements in individual countries that are specific to each device. These device specific and country specific regulatory requirements are linked to a qualified Arazy Group expert, who can review the documents provided by the manufacturer to ensure compliance.

4.3.2 How does Licensale work?

When a customer decides to initiate their product registrations, their Licensale account will be created. Each customer has their own portal that they can access from anywhere in the world. The customer can control the access to the portal (Figure 19). They can give other team members full access to the portal, or they can restrict access to one document e.g. the customer may only want the distributer to have access to a limited number of documentation. Based on

the customer's requests, Arazy Group will open an application for each device and each country they wish to access. The customer is trained on how to use the portal. Generally, the customer is advised to focus on one application when they first start using the portal.

When the customer logs into the portal, they will see their list of applications, filtered per device and country. When customer clicks on an application, the list of documents required to register their product in that specific country will appear. The application will clarify the language and legalisation requirement of each document. The customer will be able to upload their company documentation to their application and then submit the documents for review to the Arazy Group Regulatory Expert. The Regulatory Expert will be assigned based on their area of expertise i.e. they may be an expert in dealing with registrations in a particular county, or a specific device type, or a specific subject e.g. sterilization. The Regulatory Expert will be automatically notified that there is a document that requires their attention. They can reject the document if required and request more information, or they can approve the document if it meets all the requirement. It is an interactive process. When all the documents in the application have been uploaded, and approved by the Regulatory Expert, the customer can click the "SUBMIT" button. This will notify the Arazy Group Project Manager that they can download the application for submission to the Regulatory Authority.

Each time a document is uploaded to the portal, it is saved to the Documents Library. When the customer moves onto the next application, they can click the "Automatic Search" button. This will automatically populate documentation that was used in previous applications or saved to the Document Library. This saves a lot of time in generating an application. An Expert will review the documents to ensure they meet the requirements of the new country, if required. Version of documents are controlled. If the customer uploads a new version, the portal will recognise that the older version is obsolete and it will not be used in any future applications.

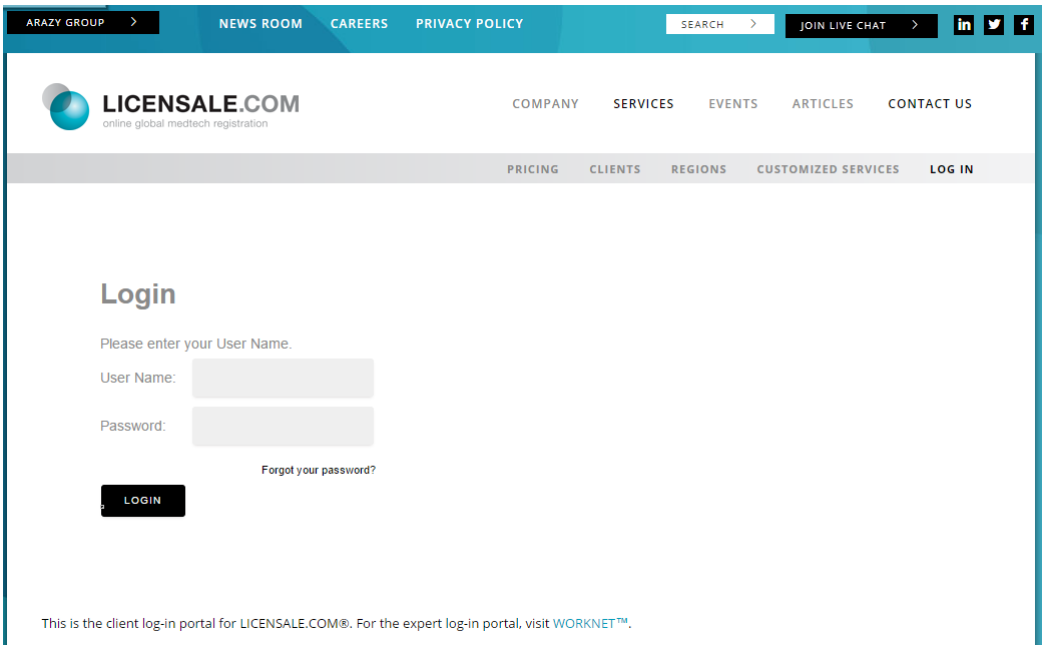

Figure 19: Clients can log-in to their Licensale Portal from anywhere in the world (Licensale 2017).

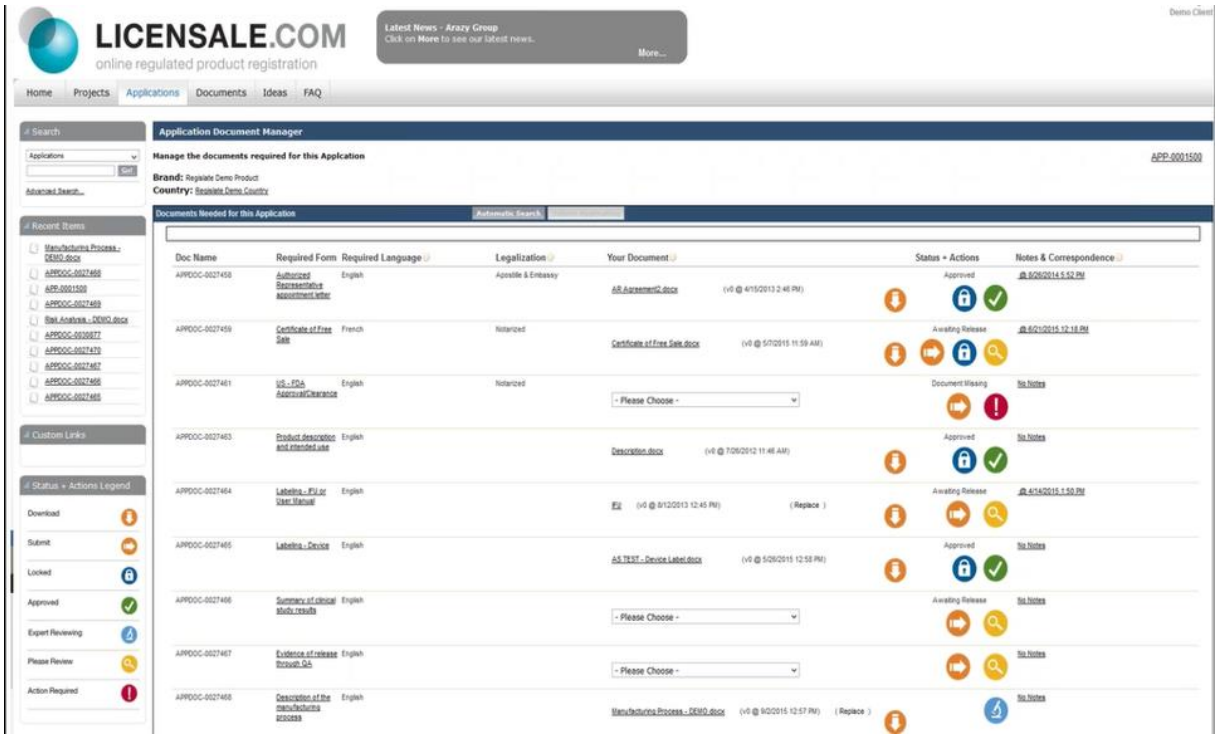

Figure 20: Sample application with list of documents required for the application, the document upload section, status of document, and notes or correspondence (LICENSALE.com 2016)

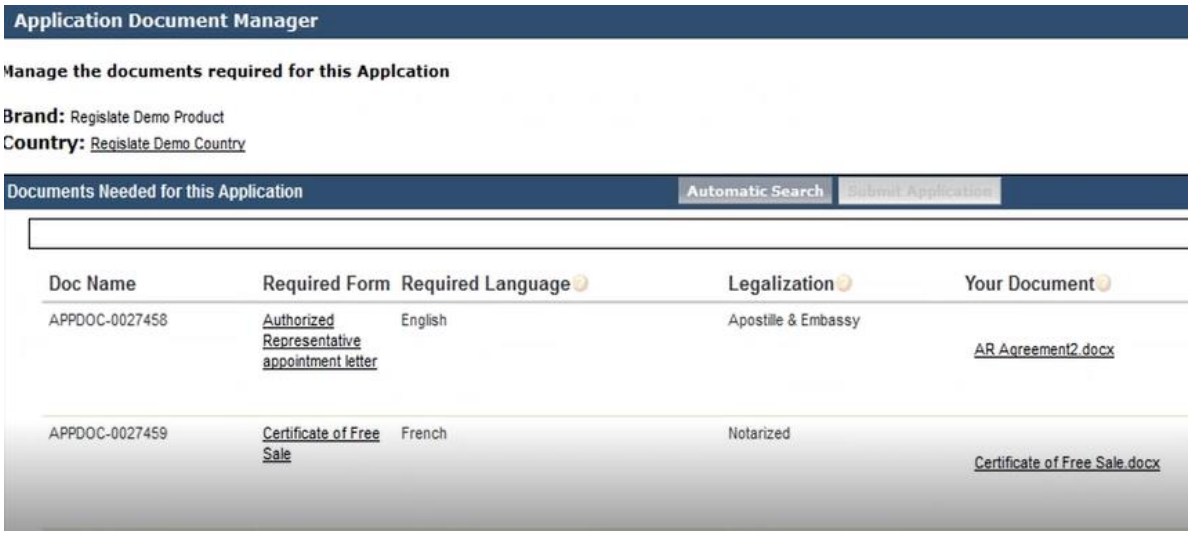

Figure 21: Document details in the application outlining the language required and legalization requirement (LICENSALE.com 2016)

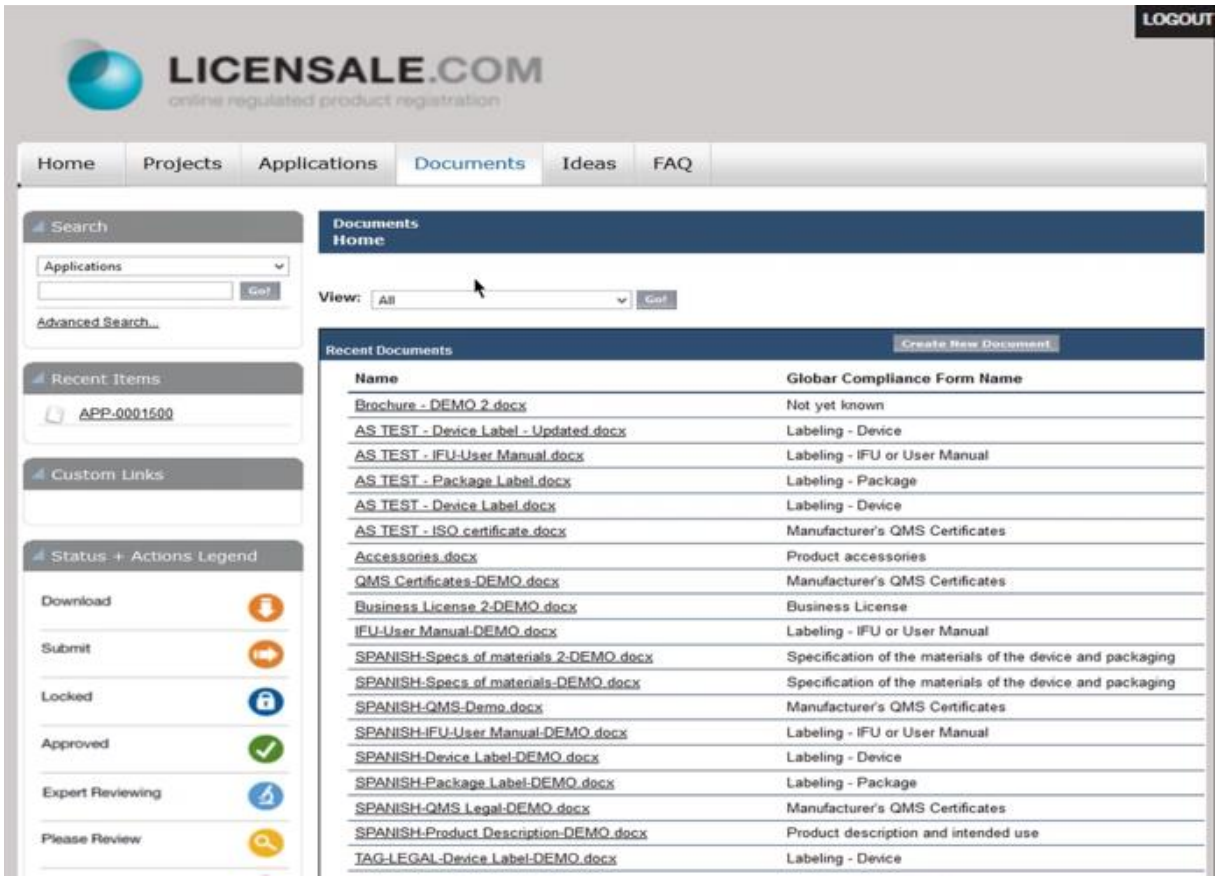

Figure 22: Sample of Documents Library (LICENSALE.com 2016).

When the product licence is approved, Arazy Group will hold the Licence on the manufacturers behalf, therefore the manufacturer maintains ownership of the product licence. The process does not end there. Licensale can also manage the post-market regulatory services, such as regulatory changes or device changes. This is a system designed to allow for alignment of the business and regulatory strategies to improve the growth of a company. The CEO of Arazy Group, sees Licensale as a tool to revolutionise product registrations and to "accelerate time-to-market by 50% for faster and equal public access to advanced Medtech products on a global scale". In 2013, a year after Licensale went live, Arazy Group published a case study on their website, summarizing the achievements of one company that used the platform (*Arazy Group - Case Study* 2017).

4.3.3 Arazy Group's Case study: "76 PRODUCTS, 16 COUNTRIES, 12 MONTHS"

In 2012, a few months prior to the launch of Licensale, Arazy Group were approached by a large human care company, which provides radiation therapy, radiosurgery, related equipment and clinical management for the treatment in oncology and neurosurgery. The company's solutions in cancer-related medical care and neuro surgery are used in 6,000 hospitals around the world, and everyday more than 100,000 patients receive treatment, or follow-up care with the help of the company's solutions. Previously, the company had focused their sales on the major markets such as Europe, North America, Brazil and China, but now they were looking to move into smaller, emerging markets. Thus, the company was faced with the challenge of expanding their regulatory intelligence within the company, with minimum demand on their regulatory team. They needed an innovative solution to this challenge, and that is where Licensale came in. The main challenge for the company was to obtain the regulatory intelligence for the specialised markets. Additionally, the company did not have a presence in these countries, which require registrations to be completed through local offices, distributors, and/or local authorised representatives. Not only did the company want to register a wide range of product simultaneously, they also needed the registration process to move as quickly as possible. The project was a high-risk project, as the devices were high-risk and high-cost, sometimes costing millions of euros; with complex installation, training and servicing requirements. It was a challenge to ensure that the registration processes ran as smoothly as possible, taking specialized regulatory requirements into consideration and availing of expedite processes where possible. The company needed to ensure the correct infrastructure and regulatory expertise was in place to obtain the market access in countries, that were outside of their usual regulatory domain.

When the registration process was kicked off, the Licensale platform was used. It allowed the company great regulatory flexibility to meet the priorities of the sales team, in the short-term and long-term. Within the first 12 months of working with Arazy Group, the company obtained market approval for 78 different types of devices in countries such as Russia, Kazakhstan, Macedonia, Israel, Egypt, Yemen, Jordan, the United Arab Emirates, Saudi Arabia, Bahrain, Cuba, and Honduras. Using Arazy Group and Licensale, the regulatory burden was significantly reduced, as otherwise this company would have had to work through numerous different registration partners, and would have had to adapt to working with their registration systems. With Arazy Group, the company could develop a relationship of trust, working with a specialised small group of regulatory professionals with similar goals and views of the importance of putting devices onto emerging markets (*Arazy Group - Case Study* 2017). Two and a half years on from their initial registration, the company had acquired 365 product registration in 20 countries, in 30 months (Figure 23*).* All of which was achieved through the Licensale platform. But how does this compare to a traditional product registration process? Is Licensale more efficient and effective?

Figure 23: Licensale Product registration comparison (ArazyGroup 2017).

4.3.4 Effectiveness of Licensale

Regulatory bodies often publish data on their review timelines but these timelines are not representative of entire product registration timeline. They do not take into consideration the time it would take to update technical documentation to meet their regulatory requirements; the time it takes to compile the regulatory submission; the time it takes to source local agents (if required); or the time it takes to addresses requests for additional information. It is difficult to quantify the time is takes to get a product approved for sale in any given country, as there are so many variable factors. Timelines and submissions requirements vary from market to market and from device to device. What may be a representative timeline for one company, could be completely different for another; depending on the how well their documentation is aligned with the applicable regulations; depending on the resources they have available; and depending on if they already have a presence in that given market. Arazy Group have estimated that a standard product registration cycle could take, on average, 110 days (ArazyGroup 2017). This figure is based on their 20 years' experience in the medical device market and it is based on their client's experience. Mr. Arazy says "the 110 days are not full-time hours, they are representative of engaging in a normal working environment, as an RA person is not solely focused on product registration. There is a lot of idle time waiting for information and feedback from different departments."

When looking at the standard medical device registration lifecycle, Figure 24 summaries what steps a manufacturer usually follows when starting a product registration in a new market, assuming they do not have previous experience in that country. The estimated 110 days takes the following twelve steps into consideration: sourcing local regulatory experts and authorized representatives; obtaining regulatory intelligence; providing compliance documents; generating missing documents/ tests/ certifications; expert review of documents for compliance; amending / translating/ legalizing documentation; preparing application dossier in line with local requirements; appointing the local representative; submitting the application to the Local Authority; responding to authority review; and finally obtaining the product license.

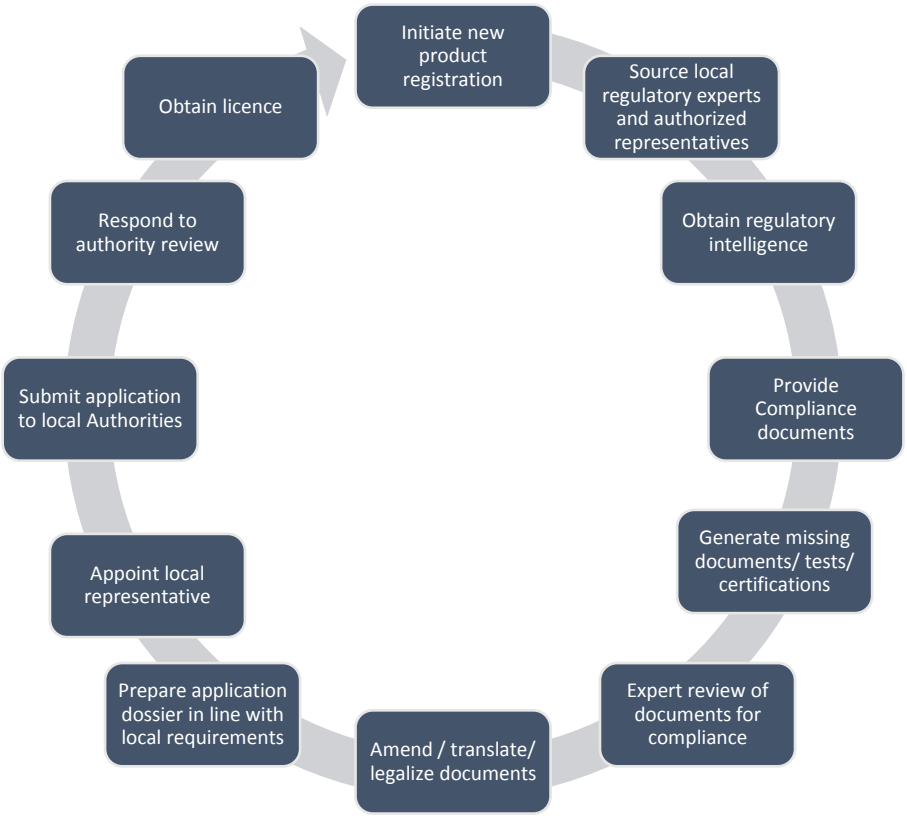

Figure 24: 12 Steps in the Standard Product Registration Life Cycle.

Arazy Group estimate that they can reduce the average 110-day standard product registration lifecycle down to an average of 40 days. Using the cloud based solution the Licensale registration lifecycle can be reduced from a 12-step process to a five-step process, as per Figure 25**.** The Licensale portal can eliminate a lot of these steps in many ways. There is already a network of regulatory experts/ authorized representatives for over 100 countries. The regulatory intelligence and compliance document requirements are built into the portal. The network of Arazy Group experts will review the documentation to ensure they are compliant to the device and country specific requirements. When the application is ready for submission to the local authorities, Licensale will automatically compile the dossier in line with the local requirements. The customer will still need to participate in select steps, such as generation of the missing documentation; amending/ translating/ legalizing documentation and responding to the authority review queries. Regardless of the whether it is the standard registration process or the Licensale registration process, the first application will always take the longest. With Licensale, the more applications the customer submits, the quicker the registration process can be. The customer's library of documentation become larger and larger, and any new applications can be automatically populated up to 75%. If the customer is registering a device in a similar territory, sometimes the registration preparation process can take as little as 10 working days e.g. if there is product registered in a Latin America country, the Spanish documents are already loaded to the portal, and the application generation process can be a very quick. Figure 27 is a comparison by Arazy Group based on the working days invested into a standard registration process, compared to the working days invested in the Licensale registration process.

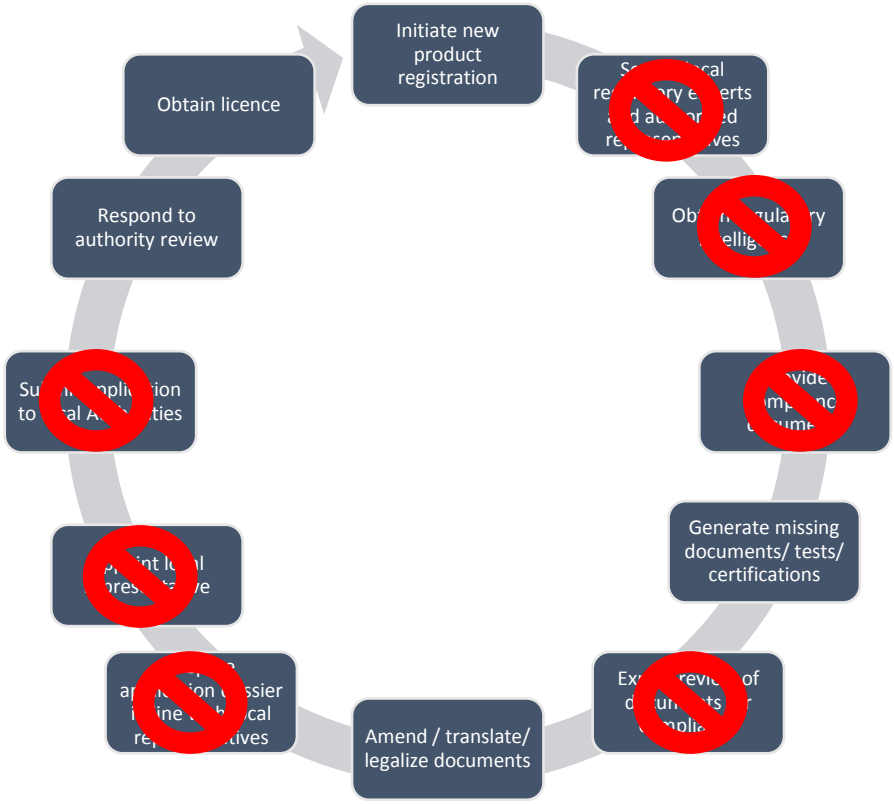

Figure 25: 7 Steps Eliminated in the Standard Product Registration Life Cycle.

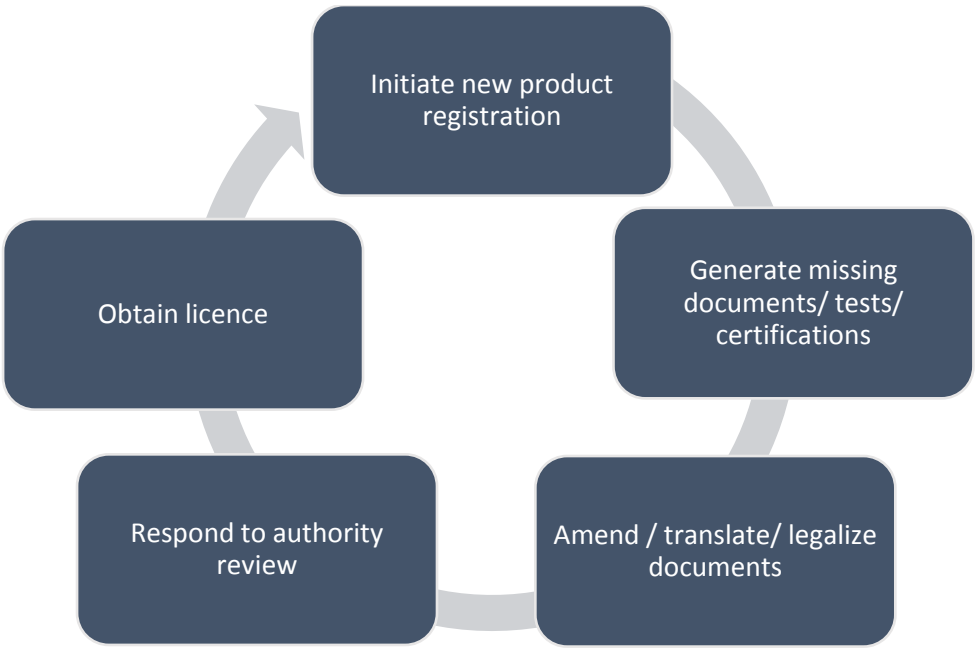

Figure 26: The Licensale Registration Life Cycle.

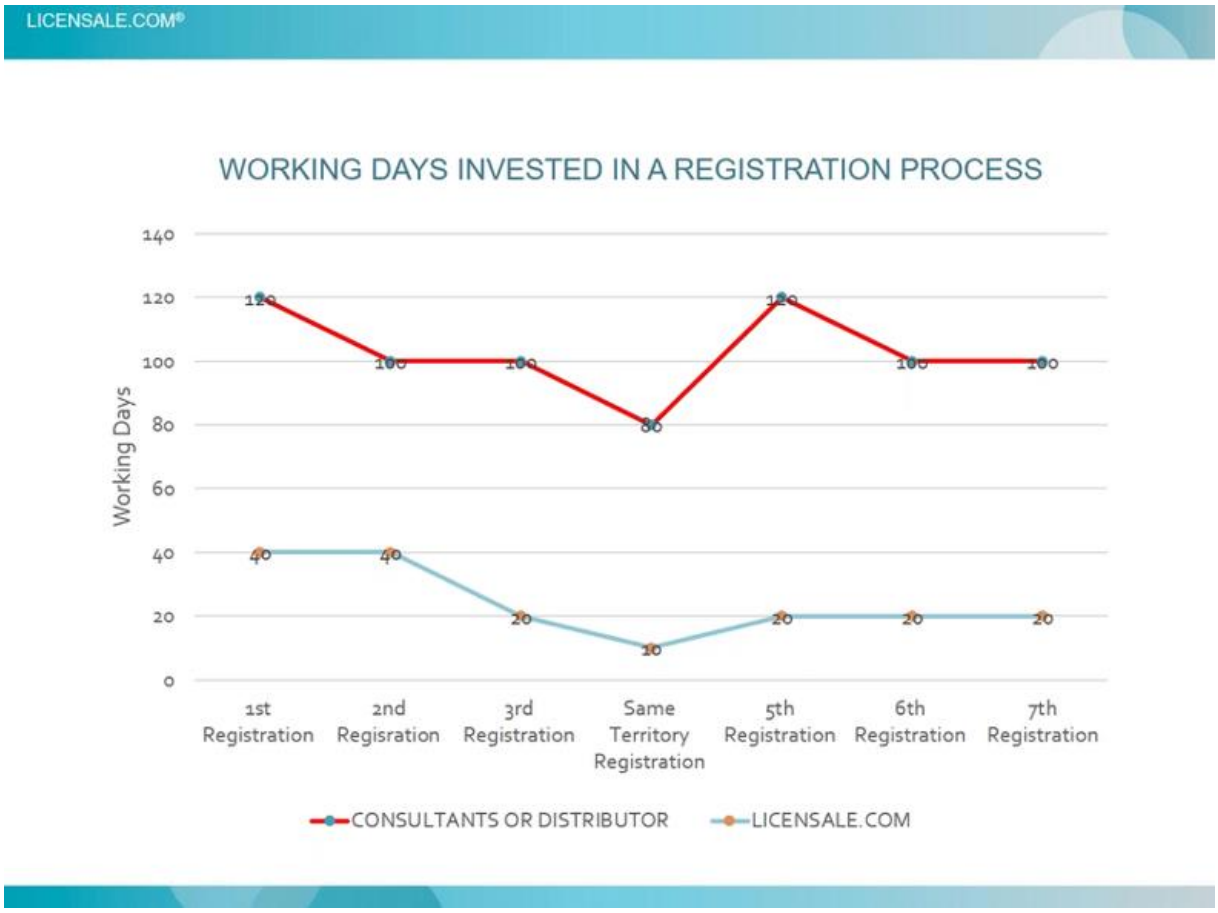

Figure 27: Arazy Group's comparison of Consultants or Distributors Vs Licensale.com (ArazyGroup 2017)

Arazy Group also claim that they can reduce the cost of a registration by up to 50%, when compared against a distributor or consultant. In a recent webinar, Arazy Group generated a model comparing the cost of Licensale against a distributor or consultancy company. The cost model was based on their own experience in industry over the past 20 years and certain assumptions had to be made. For example, the manufacturers cost associated with the work would be a minimum of €25 per hour; the distributor would charge no fee, but they would own the product licence; and consultancy fees costing half of the Licensale fee per registration. In a simple comparison between distributors and consultants over several product registrations, the consultant is always going to cost more (Figure 28). Product registration costs are lower when using a distributor because they will own the licence when the product is approved. A distributor has a lot more power and financial gains when they the licence in their name. Regardless of the actual cost associated with a distributor or consultant, Arazy state that can they can reduce the cost compared with a distributor by 20% and compared with a consultant by 30%. The percentage cost savings are increased as the number of product registrations increase, up to an estimated 50%. While these figures are estimates as very little published data, the estimated manufacturers cost are conservative. Even though the exact Licensale fees aren't published, if an assumption was made that they are double the cost, it still shows cost reduction, when compared again the more traditional model. The initial fees of Arazy Group may be a lot higher than other consultancy companies, but they save costs in other ways. As discussed above, the

manufacturer's involvement in the product registration lifecycle is significantly reduced using Licensale. It also speeds up the process. There is the potential to get a product to the market one to three months quicker than using the standard process, so that means the manufacturer is gaining revenue one to three months quicker.

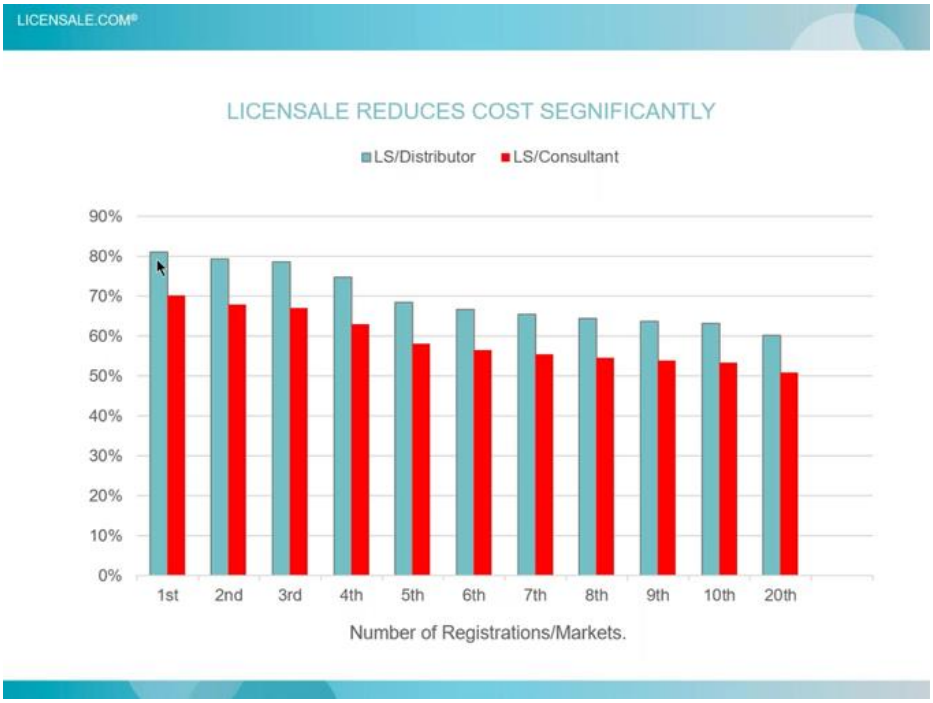

Figure 28: % cost based on number of registrations and number of market (ArazyGroup 2017).

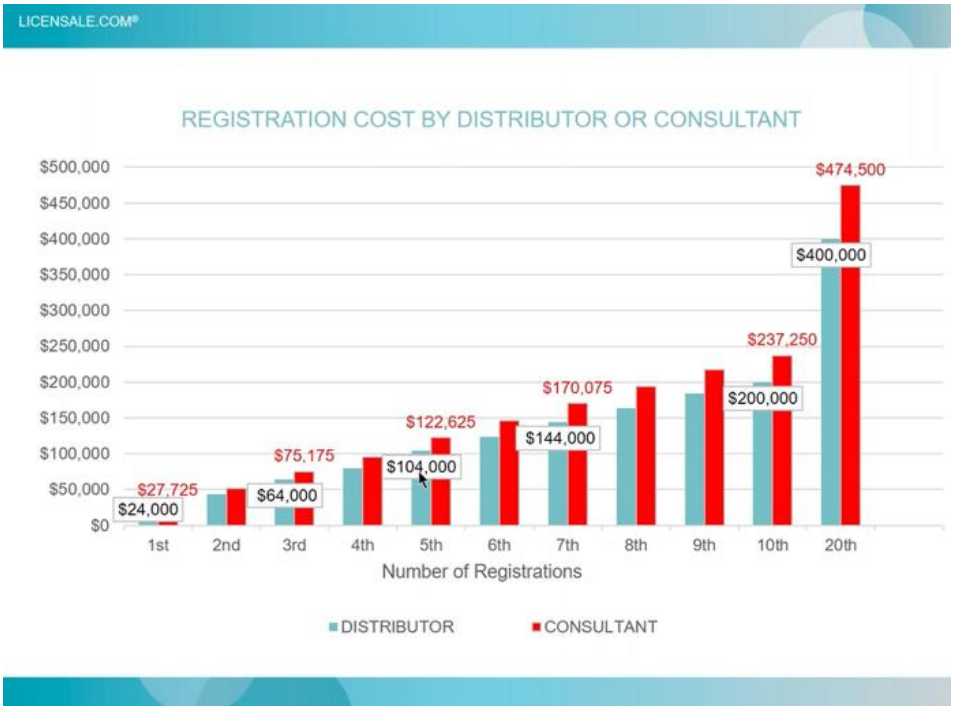

Figure 29: Estimated cost of distributor Vs consultant (ArazyGroup 2017)

Figure 30: Cost comparison of Licensale Vs Consultants/Distributors (ArazyGroup 2017).

Figure 31: Estimated cost saving over a number of product families (ArazyGroup 2017)

Arazy Group have shown they can reduce the cost and times associated with product registration by up to 50%. Taking Lean principles into consideration, the aim of lean is to reduce time and costs associated with a process by eliminating wastes and inefficiencies. Without officially using lean tools, Arazy Group have looked at the standard product registration process and reduced the cost and time by eliminating waste within the process. Licensale has reduced

over-information waste in several ways. It reduces the number of emails and document transfers, as everything is tracked through a central location. Registration requirements are clear and concise as each application is customized to the country and device compliance requirements. Auto-population of applications, reduces the duplication of information for each application. Advanced project management tools allow for information to be filtered per needs. The inventory and motion have been reduced by using one central location for all documentation. The amount of searching is reduced. The manufacturer does not need to source local agents and authorised representatives in each market, as Arazy Group have their local agents. The manufacturer does not need to source their own regulatory intelligence, as Licensale database is updated constantly with the latest regulatory requirements. The document reviews are reduced, therefore less time waiting for review/feedback on compliance documentation. Information transfer process is simplified, with the auto-population tool. Licensale automates a lot of the registration process, eliminating waste in the process. The advanced project management tools make it easier to visualise the status of application or project, making it easier to adapt market strategies quickly. Licensale also standardises the process for project registrations. Regardless of the device, country or registration type, all applications follow the same format. If a manufacturer was working with multiple distributors or consultants, the flow of work would be disrupted, as each person/group would work in different formats. It simplifies the Value-Stream Map. Also, the amount of rework should be reduced when using Licensale. Licensale is not only a software tool, it is also an expert network. The owner and CEO of Arazy Group states "the aim of Licensale is not only to submit applications quickly, but to submit successful applications".

Table 6 Types of Waste Arazy Group have eliminated

Waste	*How Licensale have eliminated waste?*
Over information	• Reduced number of emails • Registration requirements clearly outlined • Common terminology used throughout applications • Auto-population of applications. • Filtering tools.
Inventory	• One central location for documentation
Searching/Waiting	• Arazy Group already have local agents in each market. • Licensale database is updated constantly with the latest regulatory requirements. • Less time waiting for review/feedback on compliance documentation. • No more searching for documentation stored in different locations.
Complicated Transactions/ Information transfer	• Information does not need to be transferred from one submission file to another, as information will be automatically populated up to 75%. • Easier to filter information down to relevant market or device.
Process	• Licensale automates a lot of the process • Easier to visualise the progress or status of an application • Market strategy can be adapted quickly based on application progress.

Table 6 Types of Waste Arazy Group have eliminated	
Waste	*How Licensale have eliminated waste?*
	• Using Licensale eliminates the need to working with different distributers or consultants for each market so there is a consistent process standard across all applications.
Rework	• Expert review of documentation ensure applications are successful first time.
Motion	• One central location to store all documentation reduces the movement and transfer of documents.

Licensale reduces to the cost and time associated with the getting a medical device to market by up to 50%. The elimination of waste is one way Arazy Group have achieved this. There are other lean principles that could be used to explain these saving. The standard product registration life is estimated at 110 days and is said to be representative of how an RA professional will engage in their normal working environment. Although other RA professionals may not agree with the steps required for registration, they would say that 110 days is very optimistic, and that 6 months could be more of an timeframe (Jackson 2017b). In a normal working environment, there is a lot of idle time when working on product registration, waiting for feedback, waiting for the document approval, testing to be completed etc. Although there is a lot of idle time, the RA professional is never idle. Product registrations are only a part of job. They also have a constant flow of work crossing their desks every day, which include but are not limited to complaint handling, adverse event reporting, compliance work, change orders, report and protocols for review, updating legacy technical files, and updating clinical documentation. Implementing a single piece flow will always be a challenge in this type of environment, especially when you are dealing with complaints the need be responded to immediately. Arazy Group can complete their registrations in quicker timeframe because single piece flow is easier to manage in this setting. The Licensale platform can act an eKanban, automating the flow of applications to Regulatory Experts based on customer needs. Arazy Group's workload is completely driven by customer needs. They recognise the importance of having a "pull" on the process. This is why Arazy Group recommend that a manufacturer should not initiate an application within Licensale, unless they are ready to have an application approved within 40 days. In the early days of Licensale, manufacturers used to open a large amount of applications at once, even if they knew they were not ready to submit. Arazy Group found this was an inefficient way for them to work, as the Licensale Project Manager was investing time in application that could not be completed. It was an interrupted workflow. To overcome this, Arazy Group implemented the 40:20 project. This is a promise to the customer, that if they provide all the required documentation immediately, Arazy Group promise to submit their first application within 40 days of project initiation for their first application, and 20 days for every application after that. With this incentive for customers, Arazy Group can maintain a single piece workflow based on FIFO (first in, first out) (Arazy 2017).

Even though a manufacturer may not implement a system like Arazy Group, there is a lot the that the manufacturer can learn from here. There are some simple changes that a manufacturer can implement, through standardisation and kaizen. Using a standard process across all registrations can help improve the quality of work. Using Table 6, there many forms of waste a manufacturer can eliminate from the process. In the long term, there are more significant

changes a manufacturer can consider. The manufacturer should look at the systems they currently use. Most companies use multiple technologies to manage their business, such as Enterprise Resource Planning (ERP), quality management software and project management systems. Manufacturers should look at smarter ways to use these, by either building on them or merging them. Another long-term plan, could be to assess how the company manages international product registrations. The Licensale case study shows the benefits of using a consultancy company with a large international presence where possible. Also, looking at taking the product ownership away from the Distributor could be very worthwhile. Although a medical device company may not have the resources or expertise to create their own version of Licensale, this case study is proof that medical device manufacturers can be innovative with how they manage their regulatory processes. It is possible to eliminate the waste and standardise the process, and still be compliant. Licensale proves that this approach can improve compliance to regulation.

5 Chapter 5: Conclusions/Recommendations

5.1 Overview

Medical device manufacturers are facing a challenging time with global regulations becoming more complex and demanding. As the industry grows, so do the regulations. There are significant changes in global regulations for established and emerging markets. With the new European Medical Device Regulations published in the Official Journal of the European Union on 05 May 2017, all manufacturers are based in the EU or that sell medical devices or IVDs will be faced with the challenge of updating their quality and regulatory frameworks to align with the new regulations. Although the regulations are changing, there is a shift towards global harmonization. MDSAP is a very positive step forward but it is in its early stages, and it will be a challenge for companies to move to this new format of auditing. The Literature Review and the Interviews completed for this dissertation, highlight how industry is concerned over how they will manage these regulatory changes. There was a consensus across regulatory personnel that regulations are becoming more complex and maybe even unnecessarily so. It will be a challenge to implement and maintain compliance to these new regulations. Not all manufacturers have the resources to manage the changes. Instead of adding more resources, manufactures should look at ways to work more efficiently and effectively. One way for manufacturers to do this is with lean tools.

Lean concepts have been used in manufacturing for the past 70 years, to reduce waste in process, improve lead time, reduce cost and improve quality. The literature review shows lean principles can be applied across many industries, regardless of the product or service, with positive results. Despite this, there is no published evidence that lean concepts are being used for regulatory processes. Lean tools are commonly used by medical device manufacturers, for the production line and for some of the services that support production but there is hesitation to use them for regulatory processes. Feedback from the interviews would suggest this may be down the complexity of the process. It is difficult to implement lean processes and they do fail if they are not maintained correctly. The reasons for failures can be down to lack of education and training on lean tools, lack of commitment and use of the incorrect tools. The literature

review has highlighted that larger multinational companies are more likely to implement lean processes than SMEs, for fear of the cost implications. The same could be considered for regulatory processes. Manufacturers may not be extending their lean programs to the regulatory processes, due to fear of the cost implications. Failures in regulatory processes, can have severe cost implications on a business, as it can result in delays in getting product to market or even product withdrawals. However, the evidence is there to prove that using lean will improve the quality of work, not reduce it.

The case studies focused on two very different companies, each looking at ways to work more effectively. VistaMed, partnered with Freudenberg Medical, have a strong lean culture embedded in the company. Lean thinking is at the core of all decisions. While the most visible results can be seen on the production line, VistaMed expand their lean practices to the business processes. Three examples were included in this case study: the Kaizen to reduce the handovers in the purchasing components; standardization of the process for design transfer; and completing 5S on the Design History File format. The examples demonstate how lean thinking can be applied to compliance process, to improve consistency, eliminate opportunities for error, and reduce process time. Arazy Group is an excellent example of a company that have changed the way they work and have the data to prove its effectiveness. The CEO and founder of Arazy Group recognizes that if they did not develop the Licensale tool, another company would have. Regardless, Arazy Group can be seen to be ahead of the curve, combining an advanced data management tool with a wide network of regulatory experts. Like Merit Medical, Arazy Group recognises how software platforms have transformed our daily lives, so why not bring this forward to the workplace. There is a lot to be learned from the way Arazy Group have adapted to the challenges of the ever growing and ever complex regulatory environment. It is a case study that shows how the investment of time and money into a system like this can save time and money in the long term. Most manufacturers won't have the system or expertise that Arazy Group have in place but there is no reason they shouldn't be working on innovative processes like Arazy Group. The analysis of the Licensale, shows that Arazy Group used lean philosophies to improve their processes. They have standardised their processes, used visual management to make problems visible and they have eliminated many forms of waste by automating the process as much as possible. Any medical device manufacturer can do the same for their regulatory process

5.2 Limitations of this Dissertation

This dissertation does address the benefits and the challenges of implementing lean thinking for regulatory process. It also gives recommendations on how to use lean tools to eliminate waste, optimize value-added activities, reduce lead time and improve the quality of data in regulatory processes. The Arazy Group case study demonstrates that this can be achieved but the effectiveness of the data is based on assumptions as there is a lack of comparable published data. While the VistaMed Case Study does give examples of how to implement lean tools to improve compliance, they are not specifically regulatory processes. There are processes that RA could be involved in but they are not processes that would be owned by RA. There a are number of recommendations for future study or projects that can address these limitations.

5.3 Recommendations

Throughout the dissertation there have been examples on companies are using lean tools like kaizen, Just-In-Time, Kanban, Standardisation and 5S. The first step in any Lean programme is education and training. If employees don't understand Lean, they will be resistant to change the way they work. A lot of the time people don't see the wastes and inefficiencies in their system. However, if they are educated on lean principles and trained on how to use lean tools, this will change the way they look at how they work. Lean can be described as many things, a concept, a philosophy, a set of tools etc. All of which are correct, but in my opinion it is best described a culture. Lean is a set of customs, ideas and behaviours of a group of people. For lean to be successful, it should be become the culture of the company. If there is a strong commitment to Lean culture in the company, the biggest challenge is overcome. Next step is to develop a Lean program. This can be done in small stages. If a manufacturer focuses on one of their main problem areas, usually when the process is leaned out, it highlights other problem areas that they may not have been unaware of. There are many ways to start a Lean programme.

Future Lean projects could look at running Kaizen events on regulatory processes, like Technical File Generation, Complaints Evaluation, Change Assessments, Post Market Surveillance (Figure 32). If the process takt time can be reduced, this can free resources for other critical processes. Maintaining the new processes will be challenging, so the use of visuals boards are excellent ways to monitor the processes. They provide a top-level indicator of the project status and are a visual way of highlighting inefficiencies in the process.

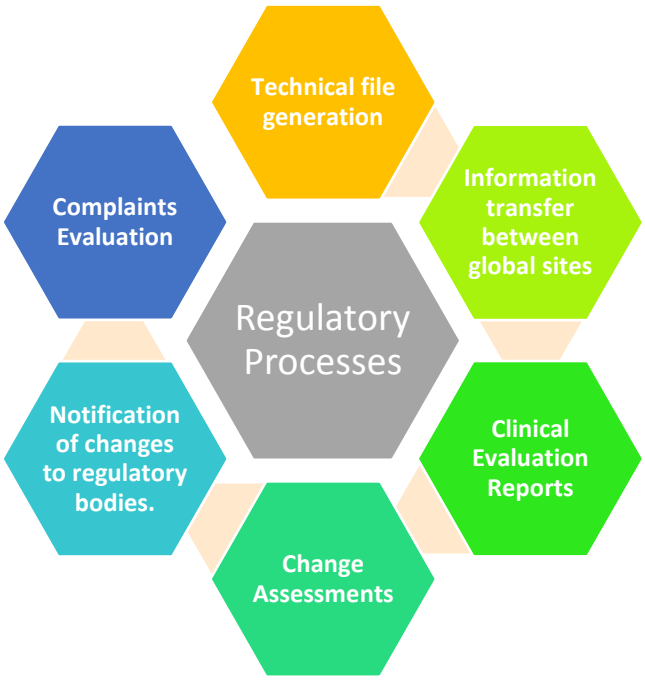

Figure 32: Potential Regulatory Process Kaizens.

The Kaizen events are a perfect opportunity to standardise a process e.g. if a manufacturer decides to focus on the improving the process of generating a Product Registration Dossier, they should structure the process so that is standardised across all regions. It may be challenging to standardise the content of the dossier, especially if there are conflicting regulatory requirements. But it is possible to standardise the format. There are many forms of standardisation. It can be achieved through decisions trees, standard operating procedures (SOPs), or system standards, for example, for education and training procedures. As shown in the VistaMed case studies, 5S is a great tool to use to aid standardisation.

Value-stream mapping is also an excellent tool to visualise the process but also show the relationship and dependence on other processes. Generating the value-stream map would be very difficult task but would be an excellent tool to aid both quantitative and qualitative analysis of the process, and would helpful in facilitating Kaizen and Standardisation. It also enables the implementation of a Kanban system, or an electronic Kanban system (eKanban), that visualizes the flow of work. Establishing the pull in the RA process, so that tasks are driven based on employee capacity and by their target completion date. It is a visual system that will assist in prioritising work. There are many ways an RA department can establish a Kanban system. The simplest being visual boards. VistaMed and Freudenberg use visual boards in many processes to track resources, work prioritisation, flow of work. A potential more complex Kanban to implement, is the eKanban e.g. using Enterprise Resource Planning (ERP) systems. ERP systems are often in used in manufacturing to show the queue of works, so there is potential to adapt an ERP system to manage RA processes e.g. complaints handling. Taking Merit Medical and Arazy Group as examples, they already have systems that show a queue of work and it was proven to be beneficial.

5.4 Conclusion

Although there are harmonisation efforts, we will never be in situation where medical devices can be shipped freely between countries. The medical device industry is changing, with a shift towards personalised medical products. If our products can be customized, then regulations should be customisable also. Going forward, Regulators must develop regulations that are harmonised and customisable. However, this is a slow process, so manufacturers need to work with the cards they have been dealt, but manage them in a smarter way. The implementation of MDSAP is an opportunity for standardisation. The EU MDR is an opportunity to rebuild processes. Instead of adding to the current processes, manufacturers should be using the EU MDR as an opportunity to transform their systems. The intent of any regulatory body or medical device manufacturer should be the same. The “intent” is that a device that is safe and effective, that performs as intended, and that is of state of the art technologies. So often manufacturers focus solely on the regulations, and can get bogged down in building a regulatory and compliance framework. If the manufacturer takes a step back from the text within the regulations, and focus on the intent of the regulations, the requirements become a lot clearer. Always bringing it back to the intent can help focus the goals. The intent is similar, if not identical, across all regulatory bodies. Instead of putting resources into a system that can be customized for each regulatory body, put the resources into developing a system that takes the commonalities and intent of all requirements and then allow justifications or tweaks to address

the additional region-specific requirements. However, it is important to recognise that the biggest challenge for all stakeholders in the medical device industry, is how to navigate through the grey areas. One of the main principle of lean thinking, is to do what is required and do no more. This is difficult when it comes to regulations, as so much is open to interpretation. Opinions differ from person to person, company to company and regulator to regulator. This is where manufacturers will rely on harmonisation efforts and consensus across Regulatory Bodies.

Manufacturers are seeing the need to adapt but the attitude is slow to trickle down to the regulatory and compliance side of things. The recognition of the need for change stems from different reasons for different manufacturers. Some companies don't have ability to pump more resources into regulatory and compliance so instead, see the need to change the way they do things. Other companies have seen the benefits of lean and six-sigma on the manufacturing line, so are willing to see if it can make improvements in other areas. Although there is an awareness across industry of the challenges of working in RA, there is a lack of perception of the need to change how RA processes are managed. There is an attitude in RA, that we need to document as much as possible to satisfy all possible scenarios of requests for more information from the Regulatory Bodies. Over-information is worst form of waste, as it hides the problems and leads to other types of waste. If patient safety is at the forefront of all decisions, RA need to look at simplifying their processes where possible. It may seem like an incremental change, but small improvements over time will lead to a better process. Looking at companies like Arazy Group, Freudenberg Medical, VistaMed and Merit Medical, they see the need for change and innovation, be it with Lean tools, advances in software applications, or both. They recognise that if they don't do it, someone else will. If a medical device manufacturer is to stay competitive in this industry, they need to be innovate and change the way they work. Yes, manufacturers are always working on innovative products, but they don't see the benefits in extending it to supporting processes. If they take this approach to their regulatory processes, they will be able to get the products to market quicker, and ultimately benefit the patient by giving them access to products that may not have been available to them. There are many ways for a company to improve their processes, but when lean tools have been proven to be so effective, why re-invent the wheel?

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