Pharmaceutical Manufacturing and Health Information Technology:
A Reflection About Lean Six Sigma and Industry 4.0

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INTRODUCTION

Health is considered a global public good. It is not exclusive, that is, that no one or any collectivity is excluded from its possession or consumption. Also, its benefits may be available to all people. There is also an apparent consensus that health is not competitive, and that there is no rivalry, that is, one person's health cannot be at the expense of excluding other people (Hartz, 2012).

Medicines are highly complex products, in a sector of intense technology and innovation. In the Brazilian health system, there is private and public production of medicines. They do not compete with each other, but are complementary, given that the public production of medicines, by Public Pharmaceutical Laboratories (LFO – Brazilian term), is mainly dedicated to diseases of no interest to private pharmaceutical laboratories (Magalhães et al., 2008b). The LFOs make up a national public heritage to produce medicines. They contribute to the supply of medicines to the public sector, especially those intended for endemic diseases that afflict the most vulnerable population, without great commercial interest for the private sector (Figueiredo et al., 2020).

The pharmaceutical sector is one of the most capital-intensive areas of the economy. In its activities, it presents relevant investments in Research, Development & Innovation (R, D & I). In this aspect, this sector is only surpassed by the arms industry (Magalhães et al., 2008a; Gadelha, 2003). The pharmaceutical industry's contribution to global health is extraordinary. By the year 2022, spending on medicines by the world population is expected to reach US$ 1.5 trillion and the sector's revenue will be about US$ 370 billion higher than in 2016. According to IQVIA Institute for Human Data Science (2022), there is a prospect for drug spending growth of around 6% by 2023, most of which will occur in developed markets driven by the areas of oncology, autoimmune diseases and diabetes. However, this industrial segment faces adversities, which drive the adoption of business strategies, such as Lean Six Sigma, widely used in almost all types of industries. The motivations for its implementation are: reducing costs, increasing profits, improving operational performance, optimizing quality, achieving competitive advantage, among others (Siregar et al., 2019).

DOI: 10.4018/978-1-6684-7366-5.ch001

Integrating Industry 4.0 with Lean Six Sigma can maximize the results that are achieved by each separate approach, providing significant gains (Filho et al., 2020). According to Arden et al. (2021), pharmaceutical companies are transitioning from industry 2.0 to 3.0, with the exception of some companies that have already adopted the latter. Destro & Barolo (2022) reports that implementation of Industry 4.0 by pharmaceutical organizations has been slow. However, regulatory agencies have been driving the use of data science, as well as the adoption of other technological innovations (Food and Drug Administration [FDA], 2019; Arden et al., 2021).

In this chapter, the fundamentals of Lean Six Sigma and Industry 4.0 are presented and the combined use of these methodologies is investigated due to their complementary relationship. Additionally, the benefits and limitations of these approaches in the pharmaceutical industry are explored, as well as the difficulties to implement them in the context of this industrial segment.

BACKGROUND

Almost two decades ago, the pharmaceutical industry began to face a series of adversities: declining productivity in Research & Development; increasing regulatory requirements; novel and more complex therapies, such as personalized medicine; increasing competition and complexity; pressure to reduce drug prices and more recently, a high number of recalls and shortages due to quality problems (Yu & Kopcha, 2017). Additionally, it was found that the performance of production processes was inferior to that of other types of industry, presenting high variability and consequently large fluctuations in cycle times; high scrap and rework rates and elevated quality costs. These challenges imposed the need to make manufacturing more agile, flexible and efficient, without increasing costs. It was necessary for the pharmaceutical industries to adopt operational excellence and continuous improvement programs, implemented long before in other industrial segments (Basu, 2010).

In 2002, the Food and Drug Administration (FDA) launched the "Pharmaceutical Current Good Manufacturing Practices for the 21st Century: a Risk-Based Approach". This initiative aims improving and modernizing manufacturing and product quality regulations. With input from academia and industry, the FDA has built a vision for pharmaceutical manufacturing and quality for the 21st century: a maximum-efficiency, agile, and flexible pharmaceutical manufacturing sector that reliably manufactures high-quality medicines, without the need for extensive regulatory oversight (Yu et al., 2016). In subsequent years, the FDA and other regulatory agencies have been participating in "International Conferences on Harmonization of Technical Requirements for Registration of Pharmaceuticals of Human Use" (ICHs) with the aim of developing guidelines to make drug regulatory processes more efficient, such as example:

a) ICH Q10: provides a harmonized model for a pharmaceutical quality system, which promotes continuous improvement throughout the life cycle of the product (Basu, 2010).
b) ICH Q12: provides a framework to facilitate the management of post-approval chemistry, manufacturing and controls changes in a more predictable and efficient manner across the product lifecycle (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH], 2021).

Adherence to the initiative and the guidelines cited is advantageous for industries as it reduces production costs and the number of defective products and guarantees greater flexibility with regulatory authorities to implement changes and improvements (FDA, 2007; FDA 2018).

Despite the efforts of regulatory authorities, a high number of recalls and interruptions in the supply of medicines, especially legacy products, due to quality problems are observed. From January 2013 to October 2018, nearly 8,000 drugs were recalled by pharmaceutical companies in the United States and abroad (Huggins, 2019). FDA initiatives also include continuous improvement to optimize quality, especially for legacy products. Lean Manufacturing, Six Sigma, as well as the integration of the two methods: Lean Six Sigma are recognized as the most used business strategies in organizations with the aim of improving processes, reducing production costs and optimizing product quality (Antony et al., 2017).

Lean Manufacturing is a management philosophy derived from the Toyota Production System. The origin took place after the end of World War II. The post-war economic crisis resulted in reduced demand and high inventory of cars at the plant, leading Toyota into financial difficulties. In 1943, Taiichi Ohno, a mechanical engineer, was hired by the automobile industry. Based on Ohno's perceptions that mass production, used in the western automobile market, generated large inventories, a high number of defects and was not able to serve clients in a customized way, he developed the fundamentals of the Toyota Production System (TPS), recognized for the ability to produce a high variety of items in small volumes, economically (Chiarini, 2013).

The Six Sigma methodology was developed in the mid-1980s by Motorola engineer Bill Smith based on his research into process capability and defect reduction. At the time, the company faced consumer dissatisfaction, who considered its products to be of low quality and fierce competition, mainly of Japanese origin. Despite the satisfactory results obtained by Motorola, the approach only became recognized after being adopted by General Electric in 1995. (Antony et al., 2017; Singh & Singh, 2020; Patel & Patel, 2021).

Over time, some organizations that had implemented Lean Manufacturing and Six Sigma approaches through standalone programs began to employ them in a more integrated manner. Other companies that had adopted only one of the methodologies began to reinforce it or expand its scope, incorporating tools from the other initiative. Although the two methods to implement improvements are different, they are convergent. Additionally, the methodologies proved to be complementary. The Lean Six Sigma program, resulting from the combination of the two approaches, incorporates the benefits of each of the methodologies, being more effective in achieving continuous improvement than each method alone (Paladini & Walter, 2019; Patel & Patel, 2021).

There is an increasing trend in research on the integration between Lean Six Sigma and Industry 4.0 (Ejsmont et al., 2020). The collection and analysis of information in real time and with high reliability and predictability enhance the results of Lean Six Sigma, whereas this latter enables a faster and more efficient implementation of Industry 4.0.

Regulatory agencies have been encouraging the pharmaceutical industry to embrace continuous improvement and data science technologies as they offer solutions to challenges faced by this sector.

LEAN MANUFACTURING

Lean Manufacturing can be defined as a methodology that aims to reduce wastes in the production system, resulting in improved performance and greater customer satisfaction in terms of quality and variety of products or services (Patel & Patel, 2021). In the Toyota Production System, wastes were classified into seven types:

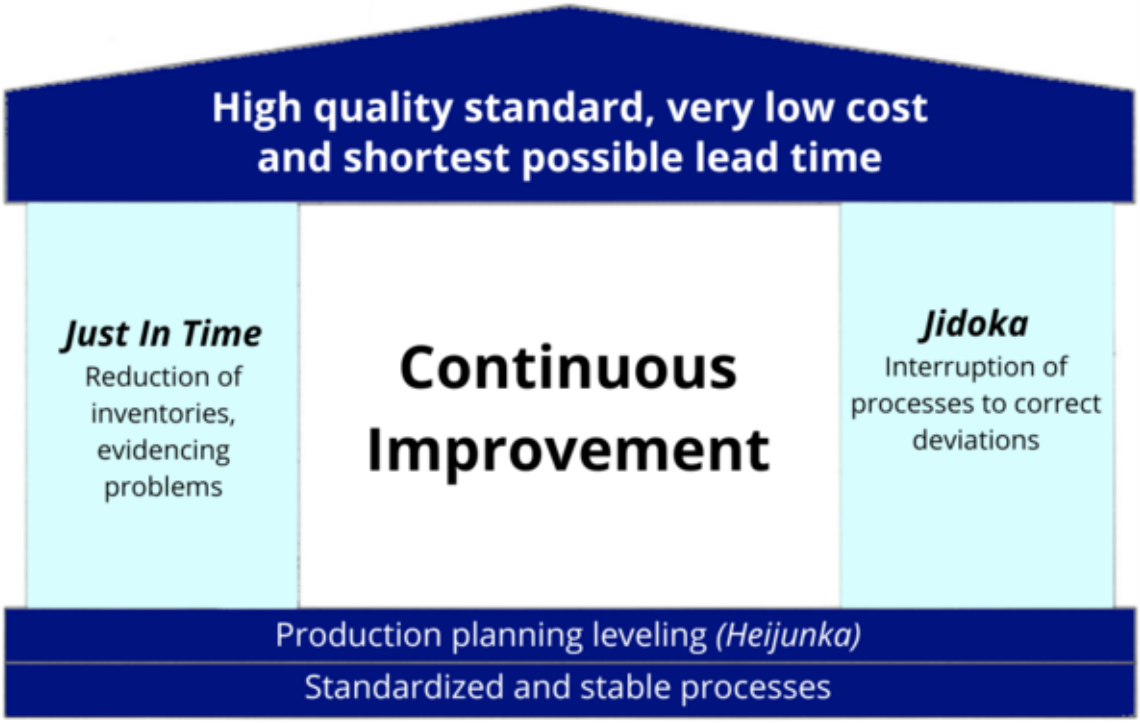
a) Overproduction: consists of production in quantities greater than required or before the products are needed;
b) Waiting: refers to the time intervals in which operators or machines do not carry out processes or operations;
c) Transport: waste of time with material movement;
d) Processing: portions of processing that could be eliminated without affecting the basic features and functions of the product or service;
e) Inventory: losses resulting from the accumulation of raw material, work in process or finished product inventory;
f) Waste in movements: characterized by unnecessary movements performed by operators in the execution of an operation;
g) Waste in the elaboration of defective products: results from the manufacture of products that do not meet the quality requirements, or the standard required by customers (Ghinato, 1996).

Another waste: products and services that do not meet customer needs, was identified by James Womack and Daniel Jones, authors of the book "Lean Thinking: Banish Waste and Create Wealth in your Corporation" (Found et al., 2015). In this book, the five principles of lean thinking have been described:

a) Specify value from the perspective of the end consumer: the first step in the philosophy is to define value accurately, in order to meet the specific requirements of end consumers. It must be defined by customers and not by companies (Jones & Womack, 2003; Werkema, 2012).
b) Identify the complete value chain of products or services: the value chain is the set of all activities required for: the development of the product, the service or a combination of the two; information management (from order to delivery) and physical transformation (from raw material to finished product, received by the customer). In general, the evaluation of the value chain makes it possible to identify 3 types of stages: those that do not create value and are expendable and can be eliminated immediately; those that do not create value but cannot be eliminated (are unavoidable) with existing technologies and production assets, and those that create value.
c) Implement continuous flow: in order to implement seamless flow from raw materials to finished products without interruptions, Taiichi Ohno and his co-workers employed techniques to reduce batch changeover time and adjusted equipment capacity to smaller batch sizes so that one operation was performed immediately next to the other, in a continuous flow.
d) Establish the customer-pull system: with continuous flow, production becomes much faster, and inventories are reduced, allowing the organization to produce what the customer wants, when they demand it. In pull production, if the customer does not place the order, no production order is issued, and manufacturing is not started.
e) Pursuing perfection: the 4 previous principles interact with each other, creating a virtuous circle. The more precise the value is specified, the closer the product is to what the customer wants. The faster the continuous flow, the more visible waste becomes in the value chain and can be eliminated. The more strained the production system, the more impediments to flow are exposed and can be removed. (Jones & Womack, 2003).

With the implementation of Lean Manufacturing in organizations in the United States and Europe, understanding of Toyota Production System has evolved and the importance of culture as an element of the system has been recognized. It was found that the incorporation of the Toyota culture is fundamental

Figure 1. Toyota Production System House Source: Adapted from Liker & Morgan (2006)



for the reproduction of the results obtained by the corporation. The Toyota Production System is a series of three intertwined elements: philosophical foundations, managerial culture and technical tools – a triangle, at the center of which is human development (Found et al., 2015).

The structure of a house is used to symbolize the Toyota Production System, as can be seen in Figure 1, being an icon of the Lean Manufacturing.

The foundation of the house is based on standardized and stable processes and on Heijunka. The latter is the Japanese word for leveling production planning so that the variety (mix) and volume of manufactured products are constant over a period. Heijunka reduces excessive production variability, making it more stable and predictable. The house has as pillars the tools: Just in Time (JIT) and Jidoka. JIT is an operations philosophy and a production planning and control method that aims to meet demand in the time required by customers with perfect quality (zero defects) and no waste. According to the approach, products and services must be produced exactly when they are needed: not before so they don't turn into inventories, nor later so that customers don't have to wait. Just in Time reduces stock levels between production stages, so that if one stage of production is stopped due to lack of materials or a machine breakdown, for example, there is no stock for the next stage to continue operating. In this way, problems are highlighted, forcing their resolution (Slack et al., 2009).

Jidoka is the pillar of quality construction focused on customers, whose concept is to do it right the first time. The detection of defective products after manufacture through an inspection system is not considered Jidoka. The simplified translation of Jidoka is autonomation, defined as "automation with a human touch". In autonomation, the human presence is minimized, and the equipment is equipped with the ability to detect the abnormalities that occur and automatically stop the process, thus avoiding the manufacture of defective products or components. Detection is a machine function, while problem

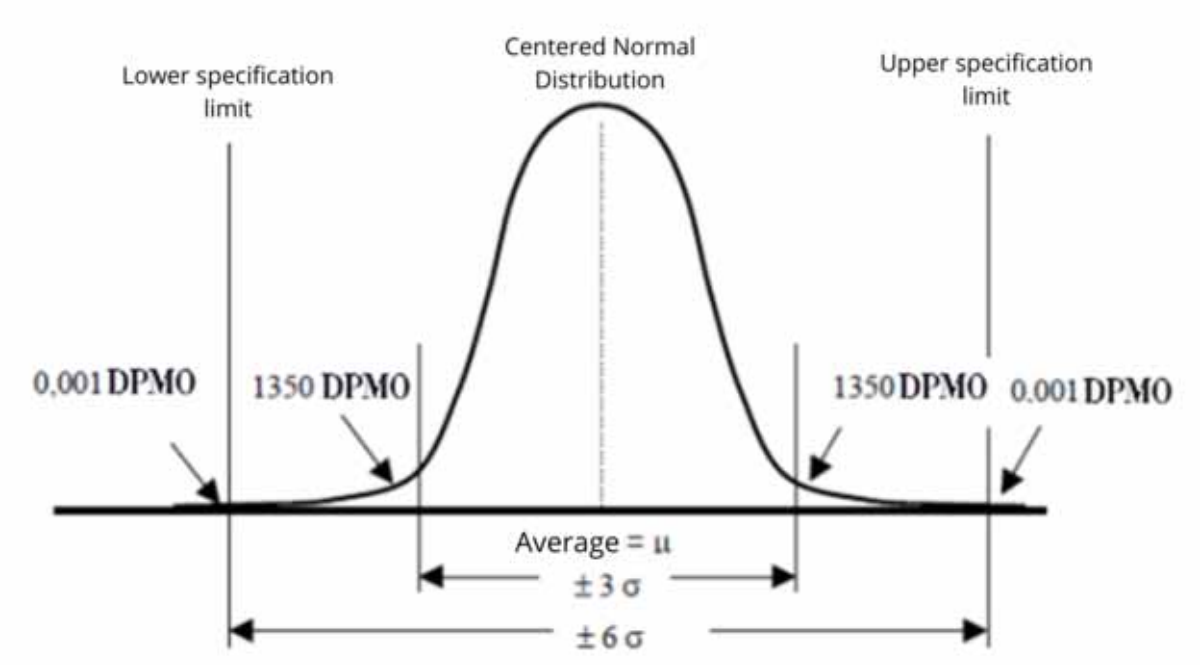
correction is man's responsibility. (Ghinato, 1996; Liker & Morgan, 2006; Soliman, 2016). Just in Time and Jidoka are approaches that expose, make visible the problems. This fact, combined with a trained and motivated team to eliminate the root causes of these problems, favor an environment in which improvement is practiced continuously. The objectives of Toyota Production System are represented on the roof of the house: high quality standards, very low cost and the shortest possible lead time (Liker & Morgan, 2006; Found et al., 2015).

SIX SIGMA

Three generations of the Six Sigma methodology are recognized with the following cores: reduction of variation and defects (1987-1994), improvement of the organization's performance through cost reduction and optimization of product development (1994-2000) and creation of value for the company and customers (from 2000). Due to this fact, several definitions of the approach based on different perspectives are found in the literature (Patel & Patel, 2021). Six Sigma is a structured approach to reduce variation in organizational processes using experts in improvement, method and performance indicators aimed at achieving the strategic objectives of companies (Antony et al., 2019).

The Greek letter sigma "σ", symbolizes the standard deviation, measure of dispersion of a data set in relation to the mean. The greater the standard deviation, the greater the variability of a process, resulting in a greater probability of defects or errors. The name of an Six Sigma process refers to the existence of six standard deviations from the mean to the upper or lower limit of the specification. The sigma scale is used to measure the quality level of a process. The higher the number of sigma's, the lower the number of defective products. In a normal probability distribution, the range between -3σ and +3σ includes 99.73% of the data, resulting in 1350 defects per million opportunities (DPMO) on each side of the curve, that is, 2700 DPMO, as can be seen in figure 2.

Figure 2. Defects per million opportunities and quality sigma levels Source: Vargas (2015)



A Six Sigma process generates 0.002 DPMO. However, Motorola noted that in the long term, the mean of the results tends to shift positive or negative 1.5 sigma, which implies 3.4 DPMO and 99.9997% conforming values. This shift is due to changes that may occur in the process resulting from design deviations, changes in raw materials and materials, wear of equipment parts, deficiency in process control, among others (KhedriLiraviasl & Tohidi, 2012).

According to Yu & Kopcha (2017), in general, pharmaceutical industry processes oscillate between two and three sigma. The authors state that the six-sigma level is rarely observed in pharmaceutical plants. The number of defects per million opportunities is correlated to the sigma level of quality and percentage of conformity, as shown in Table 1.

Table 1. Correlation between defects per million opportunities, percentage of conformity and sigma level

DPMO	% of Conformity	Quality Sigma Level
933200	6,68%	0 σ
690000	30,9%	1 σ
308000	69,2%	2 σ
66800	93,3%	3 σ
6210	99,4%	4 σ
320	99,98%	5 σ
3,4	99,9997%	6 σ

Source: KhedriLiraviasl & Tohidi (2012).
Note: values for process mean shifted from nominal value by 1.5 σ.

The Six Sigma program requires the formation and training of a hierarchically structured team. This team, made up of the company's top management, leadership, and operational employees, is responsible for conducting improvement projects and for implementing and disseminating the methodology in the company. Each hierarchical level has an assignment in the project and professionals are trained and certified according to the level of knowledge required for the role to be performed. There is no standardization for Six Sigma certification, so organizations can declare employees trained according to their own precepts (Werkema, 2012; Vargas, 2015).

The method used to conduct Six Sigma projects is DMAIC, an acronym in English for: define, measure (measure), analyze (analyze), improve (improve) and control (control). These steps are carried out sequentially and cyclically, aiming at continuous improvement. Several techniques and tools are used in the DMAIC phases, integrating the Six Sigma methodology. The following are the stages of the cycle:

a) Define: aims to clearly determine the problem, the processes involved, the scope, the preliminary project schedule, the resources needed (e.g., team members and initial investment), the goals to be achieved, the impact for internal and external customers and the expected financial return;
b) Measure: aims to better specify the problem, understand the current state of the process and identify the critical input and output variables of the process. The process inputs are the variables that supply the process, and they are the ones that, when modified, change it. The outputs are the variables that reflect the result of the process. At this stage, data must be defined and collected that allow the potential causes of problems to be discerned;

c) Analyze: aims to analyze the data measured in the previous step and the potential causes of the problem, seeking to verify the correlation between the input and output variables. In general, many probable causes are identified, and it is not feasible to collect data for all potential causes, and it is necessary to prioritize them. Then, the quantification of the degree of influence of the priority probable causes is carried out, determining the root causes of the problem;

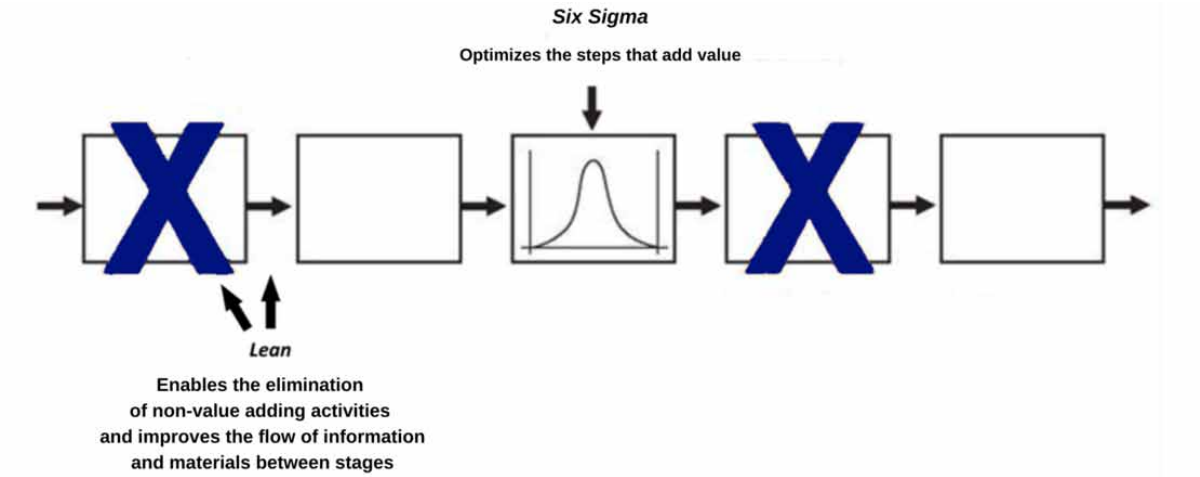
d) Improve: aims to propose, select, and implement the solution to the problem. The solution must be tested or simulated on a pilot scale. The necessary improvements and adjustments must be identified so that they can later be put into practice. After confirming that the pilot test has achieved the project objectives and that the gains achieved are in line with expectations, the solution must be implemented;

e) Control: initially, the achievement of large-scale goals must be validated and then, standardize the changes made according to the adopted solution. Subsequently, a system must be established to monitor the implemented solution and ensure the maintenance of the results achieved (George et al., 2005; Werkema, 2012).

LEAN SIX SIGMA AND EMPLOYMENT IN THE PHARMACEUTICAL INDUSTRY

Lean Six Sigma is described as "a method that aims to achieve total customer satisfaction and improve operational effectiveness and efficiency through the elimination of wastes and non-value-added activities, reducing defects and cycle time, and increasing yields, resulting in significant cost reductions" (Raja Sreedharan & Raju, 2016). In the Lean Six Sigma, Lean Manufacturing is used to improve the flow of information and materials between the stages of a process, while the Six Sigma is directed to optimize the activities that add value, comprised in the stages of the process (KhedriLiraviasl & Tohidi, 2012; Werkema, 2012; Antony et al., 2017). Figure 3 shows how Lean Manufacturing and Six Sigma interact to improve processes.

Figure 3. Integration between Lean Manufacturing and Six Sigma in process improvement Source: Adapted from Werkema (2012)



There is no single standardized model or roadmap for implementing an Lean Six Sigma program (Rathi & Singh, 2019; Vallejo et al., 2020). Organizations implement the methodology according to their needs and the way they manage it. There are organizations where Lean Manufacturing is the main program and Six Sigma is incorporated as a complementary approach in Kaizen events. In other companies it is the opposite: Six Sigma is the primary program, and the Lean Manufactuing tools are integrated with DMAIC. There are still companies in which the Lean Manufacturing and the Six Sigma are employed separately, directed to different problems, while in other organizations, the application of the Lean Manufacturing and the Six Sigma is simultaneous. One of the reasons for this diversification of methods is that some companies had already implemented one of the methodologies previously, which makes it difficult to establish a single way of integrating the approaches (Cauchick-Miguel et al., 2018).

Most of Lean Six Sigma programs employ the DMAIC method, originating from the Six Sigma, to conduct projects (Cauchick-Miguel et al., 2018; Paladini & Walter, 2019). The Lean Manufactuing and Six Sigma tools are integrated into the DMAIC stages, constituting a structured method, based on data and statistical techniques, used to improve the performance of products and processes and to achieve strategic results. There are authors who list the techniques they consider most appropriate for each of the phases of the DMAIC (George et al., 2005; Werkema, 2012;). The nature of the problems that affect products, services and processes is very variable, so the Lean Manufacturing and Six Sigma techniques to be used in improvement projects are not standardized, depending on the characteristics of the problem and the objective to be achieved (Antony et al., 2017).

Just as there are organizations that are successful in using Lean Six Sigma, there are others that aren`t. Several elements can lead to an unsuccessful Lean Six Sigma implementation. Additionally, many companies fail to sustain good initial results in the long term (Sony et al., 2020; Gaikwad et al., 2020). For these reasons, some authors have dedicated themselves to identifying barriers and critical success factors (CSF) of the methodology. Gaikwad et al. (2020) listed 16 barriers to Lean Six Sigma, among which is insufficient financial resource for implementation and training, especially in the case of small and medium-sized companies. Another obstacle to the approach is resistance to changes. Continuous improvement projects presuppose changes in usual practices. Therefore, people's resistance to changes is a barrier to the implementation and sustainability of the Lean Six Sigma program. Sony et al. (2020) identified 12 CSF of the methodology, one of them being the connection of Lean Six Sigma with customers. Finding solutions that meet customer needs is an important requirement for a successful business strategy. Lean Six Sigma should be used to translate customer demands into products, services and processes, creating value.

The Lean Six Sigma methodology is adopted in several industrial sectors: automotive, electronics, semiconductor, marine, oil and gas, textile, construction, food, chemical, pharmaceutical, etc. It is also used in the area of services: financial, public, insurance, information technology, health, education, among others. It is applicable from small companies to large organizations, from industries with manual operations to highly automated ones (Raja Sreedharan & Raju, 2016; Kant et al., 2018; Rathi & Singh, 2019). Lean Six Sigma generate many benefits in both manufacturing and service industries.

Several benefits of employing the approach in manufacturing are cited in the literature: reduction of cycle time, lead time and inefficiencies; increased capacity and robustness of processes; reduction of inventories and operating costs; increase in corporate revenues; improvement of employee motivation and safety at work; reduction of defects in processes; improved productivity and increased customer satisfaction (Kant et al., 2018; Rathi & Singh, 2019).

The Lean Six Sigma methodology is recognized for optimizing the organizational performance of pharmaceutical industries, however, it requires adaptations to the specifics of this productive sector, especially compliance with regulatory requirements (Sieckmann et al., 2018; McDermott et al., 2021).

Medicines present intrinsic risks due to its nature: adverse reactions, medication errors, intoxication, therapeutic ineffectiveness and drug interactions. Risks are also added throughout the various activities involved in the drug life cycle, which includes pharmaceutical development; technology transfer from development to manufacturing and between different manufacturing sites; commercial production and product discontinuation. In order to prevent and minimize risks and protect people's health, regulatory agencies draw up strict technical-sanitary regulations, which must be duly complied with by the pharmaceutical industries (ICH, 2009; Vieira et al., 2013).

Regulatory authorities establish Good Manufacturing Practices (GMP) guidelines as the minimum requirements for facilities, methodologies and controls used in the production of medicines. Adherence to the GMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. (FDA, 2021). Many activities performed to comply with GMP cannot be eliminated but would be considered waste in other industrial segments. Examples are records, identifications, segregations, inspections and conferences.

Manufacturing processes should be designed and controlled to ensure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Manufacturing operations interact heavily with pharmaceutical quality system practices: analysis and release of raw materials, packaging materials, intermediate and bulk products; in-process controls; change controls; investigations into deviations and nonconformities; implementation of corrective and preventive actions; validation and qualification of processes, equipment and systems, etc. These activities end up causing interruptions and waits in production, making it difficult to adopt the continuous flow required by the Lean Manufacturing philosophy (Stratton, 2004).

Medicines cannot be manufactured or marketed without being registered with the competent sanitary surveillance agencies. The purpose of the registry is to ensure that effective products are provided to the population and that meet the therapeutic purpose. Changes after drug registration that impact the composition of products, production processes, analytical methods, equipment, facilities, and procedures must be evaluated for potential risks before implementation. These changes include those arising from Lean Six Sigma projects. The pharmaceutical quality system has as one of its elements change management, defined as a systematic approach to proposing, evaluating, approving, implementing and reviewing changes (ICH, 2009). Change control is a formalized system whereby qualified representatives from the appropriate areas review proposed changes or changes that may affect the validated state of facilities, systems, equipment or processes. The objective is to determine the need for actions to ensure and document that the system is kept within the validated state (Agência Nacional de Vigilância Sanitária, 2019). According to the potential impact of changes resulting from Lean Six Sigma projects on the quality, safety and efficacy of the drug, regulatory standards may require physic-chemical analyses, process validation, stability studies and analysis and prior approval from regulatory authorities. Often, the costs and time required to implement changes end up making improvements from Lean Six Sigma unfeasible (Bellm, 2015). In a case study published in 2021, the use of Lean Six Sigma in a pharmaceutical industry made it possible to identify the action that would eliminate the root cause of the problem investigated. However, the authors reported that one of the reasons that prevented the adoption of the necessary change was the long and costly regulatory submission (Byrne et al., 2021).

Literature describes benefits achieved with the use of the Lean Six Sigma methodology in the pharmaceutical industries. Chatterjee (2014) reports the case of a company, which even producing 24 hours/

day, 7 days/week, could not meet the demand for a transdermal product. The adoption of Lean Six Sigma in this company made it possible to increase the line's productivity by 61% (from 1.3 million units/week to 2.1 million units/week), increasing capacity. Converting to financial values, the benefit represented an increase in annual sales of 41 million dollars. In a case study carried out in a biopharmaceutical industry, the application of Lean Six Sigma showed that 54% of the cycle time was composed of activities that did not add value. After the implementation of the improvement project, the cycle time was reduced by 45% (Ismail et al., 2014). A case study was carried out at a pharmaceutical plant that produces Acetaminophen tablets and had orders backlogged due to increased demand due to the SARS-CoV-2 pandemic. With the use of Lean Six Sigma, waste in the drug packaging line was minimized, generating savings of approximately half a million dollars (Byrne et al., 2021).

INDUSTRY 4.0: INTEGRATION WITH LEAN SIX SIGMA AND ADOPTION IN THE PHARMACEUTICAL SEGMENT

Industry 4.0 emerged in 2011, in Germany, with the aim of improving manufacturing competitiveness and became synonymous with the fourth industrial revolution (Steinwandter et al., 2019; Ejsmont et al., 2020). Data science technologies support the optimization of productivity, quality, customer satisfaction, energy performance indicators, lead time and costs (Skalli et al., 2022). For pharmaceutical companies, Industry 4.0 represents not only a competitive differentiator, but also a means of confronting current adversities. The use of data science technologies in experimental design, data-driven decision making and process optimization, as well as the application of predictive tools in the estimation of difficult-to-measure variables, contribute to increasing the efficiency of the development and manufacturing processes of medicines, in line with FDA initiatives, which advocate the use of more scientific perspectives and innovative technologies in the pharmaceutical segment (Steinwandter et al., 2019).

In this sense, Industry 4.0 describes the transition from centralized production to very flexible and self-controlled production. Within this production, whether the products, or all systems affected, and even all stages of the engineering process, they are digitized and interconnected to share and transmit information and distribute this information along the value chains, both vertical and horizontals and beyond in extensive value networks (Ejsmont et al., 2020).

The existence of key Industry 4.0 technologies has been suggested in the literature: Cloud Computing (CC), 3D printing, Cyber-Physical System (CPS), Internet of Things (IoT), Internet of Services (IoS) and Big Data (BD) (Ejsmont et al., 2020). Inuwa et al. (2022) describe as main components of Industry 4.0: CPS, IoT, CC, BD, Artificial Intelligence (AI), IoS, Blockchain Technology (BT), Additive Manufacturing (AM) and Smart Manufacturing (SM).

The paradigm shift brought about by Industry 4.0 is guided by new technologies, but substantially disregards the human aspects. Industry 5.0 emerged as a complement to Industry 4.0, with the aim of promoting the optimization of industrial processes, without harming socioeconomic and environmental performance. Industry 5.0 is characterized by the synergy between humans and autonomous machines, that is, by the participation of people and machines in a collaborative work environment. They also constitute pillars of the 5.0 industry: the centrality of the human being, sustainability and the bioeconomy (Nascimento & Werner, 2021; Jafari et al., 2022).

Several researchers have demonstrated the complementary roles of Lean Six Sigma and Industry 4.0 in reaching higher levels of operational performance (Tortorella et al., 2021; Bokhorst et al., 2022). The statistical techniques used in the Lean Six Sigma guide decisions about the operational performance

of companies. Industry 4.0 makes decision-making at each stage of DMAIC more agile and assertive (Gunasekaran et al., 2020). The Lean Manufacturing principles: elimination of waste, organization, standardization, and transparency are essential for the implementation and consolidation of data science technologies. On the other hand, the evaluation of detailed data of the processes generated in real time allows the elimination of all types of waste (Naciri et al., 2022). Some research has concluded that Lean Manufacturing is a prerequisite for Industry 4.0. These studies argue that waste must be reduced and activities that add value must be optimized, favoring continuous flow before processes are automated, which avoids unnecessary costs (Chiarini & Kumar, 2021; Bokhorst et al., 2022). On the other hand, there are studies that describe that Industry 4.0 must be previously adopted because the application of data science technologies enhances Lean Manufacturing results, for example through real-time data collection (Naciri et al., 2022).

Lean Six Sigma projects generate a high amount of data based on the historical survey of the problem or opportunity for improvement; assessment of all potential causes of the problem; proof of the root cause; testing and combinations of solutions and monitoring the improvement implemented. Data science technologies supplement the Lean Six Sigma as they allow more agile and human error-free data collection, as well as the analysis of large amounts of data in a more reliable, faster and predictable way. Industry 4.0 enables for more real-time data generation through sensors and cloud-based manufacturing, for example. This data supports Lean Six Sigma projects (Gunasekaran et al., 2020). Table 2 presents examples of impacts of data science technologies on Lean Manufacturing (Ejsmont et al., 2020; Naciri et al., 2022).

Table 2. Data science technologies and impacts on lean manufacturing

Data Science Technologies	Impacts on Lean Manufacturing
Cyber-Physical System, Radio Frequency Identification e Internet of Things	Favor the exchange of information between suppliers, producers and customers, reducing lead time and response time to consumer complaints
Big Data	Contributes to improving the performance of the production system
Sensors, embedded devices and software's	Enable faster changeovers
Internet of Things	Simplifies the use of Just in Time
Predictive algorithms	Facilitate automatic maintenance
Big Data and Data Analytics	Contribute to Value Stream Mapping procedures and streamline troubleshooting
Cyber-Physical System and Radio Frequency Identification	Enable the monitoring of production data in real time, making production management more agile and efficient. These two data science techniques also provide real-time access to work in progress and finished goods inventory quantities and locations
Cyber-Physical System	Contributes to the use of Andon and Kanban 4.0 as well as other production flow control techniques. Additionally, it identifies faults that require maintenance and automatically signals the responsible department in real time, corroborating to Total Productive Maintenance
Smart devices, Big Data, Cyber-Physical System and Data Analytics	Enable collecting data, calculating and monitoring Key Performance Indicators in real time
Real-time Quality Assurance analysis results	Favor Jidoka
Digital standard operation procedures associated with cloud technology and Augmented Reality	Contribute to the lean principle of standardization
Sensors, Virtual Reality and Augmented Reality	Improve safety conditions at work

Source: created by the author

Regarding the combination of Lean Six Sigma and Big Data, the analytics tools of Lean Six Sigma simplify extracting key insights from Big Data (Arcidiacono & Pieroni, 2018) and this latter allows the diagnosis of problems, the performance of predictive analysis based on data patterns and the association of the consequences of analytical results with the optimization of processes. (Gunasekaran et al., 2020).

Some authors suggest Industry 4.0 techniques to be used in each step of the DMAIC. For example, Gunasekaran et al. (2020) recommends the use of "text mining" and "video mining" in the "define" phase. Arcidiacono & Pieroni (2018) indicates the use of Internet of Things in the "analyze" step to streamline the process of verifying the root causes of a problem.

Most of the data science technologies employed in pharmaceutical companies are basic and are applied only for monitoring and analysis. Algorithms are rarely part of real-time control loops and are used for essential decisions. Many algorithms are generated in the academic context, being inadequate to the needs of industries, which in turn do not have time, resources or trained professionals for development (Steinwandter et al., 2019).

Some Industry 4.0 initiatives in the pharmaceutical segment are described in the literature. Examples of Artificial Intelligence in use in pharmaceutical companies are vision systems that allow images analyzed by software to be compared to images of standards that meet quality requirements, resulting in the rejection of products with deviations. That's how vision systems that have replaced human inspection of blisters, bottles and capsules work. These systems are also used for data integrity improvement, continuous process quality assurance and predictive equipment maintenance (Arden et al., 2021). Machine Learning has been applied in the formulation of drugs produced by 3D printing, in the optimization of controlled release mechanisms and in the prediction of pharmacokinetic parameters as well as drug interactions. Blockchain Technology was used to develop a tracking platform capable of attesting to the authenticity of the drug and verifying its location in real time from unique identifiers generated for each package (Trenfield et al., 2022).

Pharmaceutical companies face several challenges in implementing Industry 4.0. One obstacle is the lack of financial resources for the required investments. There are also technical barriers. It is necessary for organizations to have an advanced data and computing framework that combines hardware and software to provide information about products and processes in an agile way. To enable full integration and digitalization of production plants, the hardware and software of the systems of all departments must be compatible and communications must take place through networked devices. Additionally, the digital industrial environment requires a cybersecurity framework. Knowledge beyond that currently used in the pharmaceutical industries is required for Artificial Intelligence employment, and it may be necessary to hire data scientists, systems and computer engineers, and information technology and Artificial Intelligence specialists. Cultural changes and user development programs are also required. Artificial Intelligence based techniques require training a model with real historical data from advanced manufacturing methodologies, such as continuous manufacturing. Machine learning would be simpler if pharmaceutical companies shared this historical data. Thus, companies would need to abandon the current business model in which all data and knowledge are kept within each company, opting for a collaborative or open innovation model.

The regulatory challenges, specific to the pharmaceutical segment, are the ones that most impact the adoption of Industry 4.0. There is no precedence, definitions, or regulatory guidance for implementing data science technologies. In this uncertain scenario, pharmaceutical industries prefer not to take risks or spend financial resources and remain awaiting the initiative of competitors and the reaction of the health authorities. Regulatory approaches should be developed to accommodate the coexistence of industry technologies 2.0, 3.0, 4.0 and 5.0. The requirements must consider new technologies. but must

not compromise the supply of medicines produced according to Industry 2.0. Additionally, the ideal would be having a global harmonization of the rules of all regulatory bodies (Arden et al., 2021). Much of the regulations were designed with a focus on traditional drug manufacturing systems and for a single pharmaceutical quality framework, so cooperation between companies, academia and regulatory agencies is required to standardize the use of data science technologies. The FDA has already taken the first action. It lauched an initiative to identify and implement needed changes in the regulatory structure to enable advanced manufacturing technologies, defined as new medical product manufacturing technologies that can improve drug quality, address shortages of medicines, and speed time-to-market. Examples of advanced manufacturing technologies are 3D printing, modern automation and control systems for product quality and high technology and computer-controlled production facilities (FDA, 2019; Arden et al., 2021). Steinwandter et al. (2019) also pointed out the regulatory requirements as adversities for the use of data science in the biopharmaceutical segment. The implementation of Industry 4.0 is hampered because regulatory standards establish that significant changes require processes to be validated again. Additionally, the authors identified the following challenges:

- Disregarding of data science when production facilities and manufacturing software are designed;
- Absence of adequate data formats and standardized interfaces;
- Conservative Information Technology/Operational Technology Infrastructures;
- A small number of experiments compared to what is required by statistical and data science methods. This small number of experiments is due to the accelerated process development, fast clinical trials, complex processes with high production costs and risks of unsuccessful batches;
- Very long-time interval between the creation of an algorithm and its execution with production data;
- Very strict knowledge and information protection systems, which make it difficult for engineers and scientists to extract value from data.

FUTURE RESEARCH DIRECTIONS

The FDA, as well as other regulatory agencies, have driven profound changes in the pharmaceutical industry, among which continuous improvement and data science technologies stand out, which, when integrated, can provide very expressive results. It is understood that these changes will occur in the long term. In the case of Industry 4.0, it will be necessary to internalize knowledge not currently used, adapt and replace facilities and equipment and improve the regulatory framework, in order to contemplate data science. For pharmaceutical processes to reach level six sigma, quality management maturity is needed, defined as the state attained by having consistent, reliable and robust business processes to achieve quality objectives and promoting continuous improvement (FDA, 2022). Studies that monitor the evolution of the adoption of initiatives promoted by regulatory authorities would be of great value to point out strategies, difficulties and successful experiences.

Future research topics regarding the integration of Lean Six Sigma and Industry 4.0 include: (a) empirical studies, rarely found in the literature; (b) development of guidelines and roadmaps for the simultaneous implementation of the two approaches; (c) definition of critical success factors and barriers to the concomitant adoption of the two methods and (d) connections with other management strategies, such as Green and Agility (Ejsmont et al., 2020; Skalli et al., 2022).

The growing trend of using data science in the pharmaceutical industry is due to:

- regulatory agencies that have encouraged the use of advanced manufacturing technologies;
- the optimizations that can enable pharmaceutical development and manufacturing;
- technologies that can address the growing interest in more specialized and customized medicines, such as 3D printing;
- the improvement it can provide in the performance of the entire pharmaceutical supply chain (Saha et al., 2022).

Studies are needed to map the profile of technical knowledge required to prepare the workforce of the pharmaceutical industries (including pharmacists in graduation) for the advancement of technology in the factories.

Steinwandter et al. (2019) listed Industry 4.0 themes that will be evolving in pharmaceutical companies: (a) systems with open data formats and capable of communicating with other systems, facilitating the work of data scientists; (b) frameworks for defining the data science infrastructure in the form of code versions, allowing fast feedback loops; (c) systems that allow testing of sophisticated tools, such as virtual clones of manufacturing facilities and (d) knowledge management tools that enable researchers to store knowledge as models, algorithms, or documents.

The trend is that the implementation of data science technologies in pharmaceutical companies will continue to evolve and reach the human-machine integration, characteristic of Industry 5.0. The latter focuses on human centrality, benefits not only patients, but also aims to avoid the elimination of human labor from industries through education, having an economic and social nature.

CONCLUSION

Information technology is paramount to all areas of science and technology. For the healthcare industry, specifically the pharmaceutical industry, it is no different. Health information technologies have been shown to be useful for process management, reliability in quality controls and information speed. Therefore, combining quality tools with information technologies has proved to be effective for knowledge management in organizations.

The current pharmaceutical market is characterized by several challenges, such as: long and costly Research & Development; inefficient manufacturing processes; strict regulatory system; high occurrence of recalls and drug shortages; complexity of new therapies, such as cell and genetic treatments and individualized medicine. Regulatory agencies recommend continuous improvement and the modernization of pharmaceutical development and manufacturing as solutions to some of these challenges, despite historically, regulatory rigor has been seen as an obstacle to continuous improvement and innovation.

The adoption of continuous improvement requires changes that can be time-consuming and costly due to regulatory impact. In the case of innovative technologies, limited knowledge, especially about their effects on the safety and efficacy of medicines, can delay the approval of regulatory authorities (FDA, 2017). In 2002, the FDA started a program to improve and modernize the quality and manufacturing regulations of pharmaceutical products, which continues to evolve, and which has been responsible for relevant initiatives, aimed at implementing continuous improvement, quality risk management, process analytical technology, continuous manufacturing, emerging technologies, among others (Yu et al., 2019).

The integration of Industry 4.0 to the Lean Six Sigma is recognized as potentially fruitful due to the complementarity of the approaches. The elimination of waste, promoted by Lean Six Sigma, avoids spending on automating activities that do not add value. Industry 4.0 provides agility and reliability in

collecting and processing large volumes of data, reducing the time between identifying an improvement and its implementation. The use of the Industry 4.0 in the pharmaceutical segment is particularly relevant as it offers solutions to challenges faced by the pharmaceutical industry, such as: time-consuming and expensive research and development and inefficient production processes (Steinwandter et al., 2019). FDA launched an initiative to identify and implement needed changes in the regulatory structure to enable advanced manufacturing technologies, such as policy and regulatory topics related to the management of data-rich environments, the evolving concepts of process validation for advanced manufacturing systems, and the regulatory oversight of post-approval changes for these systems (FDA, 2019; Arden et al., 2021).

The pharmaceutical processes are still far from the six-sigma standard of quality, ranging between two and three sigma. In the case of Industry 4.0, it is observed that it is necessary to expand knowledge in industries and regulatory bodies, harmonize regulatory requirements and define procedures to deal with changes that impact the validated state of facilities, equipment and processes. Despite these facts and the necessary financial investment, the increase in the sigma level of pharmaceutical processes, the adoption of Industry 4.0 and other technological innovations will enable significant gains for companies: more efficient and robust development and manufacturing processes, real-time information and more affordable, less waste, more flexibility from regulatory agencies and more satisfied patients with the highest quality of medicines.

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KEY TERMS AND DEFINITIONS

Big Data: Massive amount of data, in different formats, that grows exponentially and that requires technologies capable of carrying out extensive and timely analysis.

Continuous Improvement: Philosophy that aims to optimize the company's performance, based on small and continuous changes, which over time produce sustainable improvements. It involves all employees working together in the development and implementation of improvements.

Cyber-Physical System: Integrated systems of computing, communication, and control through networks and physical processes.

Internet of Things: Interconnection of physical objects with the internet through built-in sensors, enabling the exchange of data.

Operational Excellence: A state of elevated level of maturity and measurable success in four dimensions: culture, continuous improvement, organizational alignment, and results.

Value: Worth of a product or a service in the perspective of customers and reflected in its selling price and market demands.

Wastes: Activities that absorb resources but do not create value.