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Article

Analysis of Lean Six Sigma Use in Pharmaceutical Production

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Over the last years, pharmaceutical industries have adopted continuous improvement and operational excellence programs to optimize processes, improve quality and reduce operational costs. Worldwide, Lean Manufacturing (LM) and Six Sigma (SS), as well as the integration of the two methods: Lean Six Sigma (LSS) are the most used approaches in the continuous improvement of industries and services. This work aims to investigate the employment of the Lean Six Sigma methodology in the productive areas of pharmaceutical companies located in Brazil. Interviews were conducted with managers of pharmaceutical industries that apply the approach. The results indicated the greater use of Lean Manufacturing tools compared to Six Sigma and the influence of specific peculiarities of the pharmaceutical industry on the benefits that are achieved with the use of Lean Six Sigma. The approach is considered of great value as it provides substantial benefits to the pharmaceutical industry. It is concluded that the work corroborates to the theoretical and empirical knowledge about the methodology use in the context of Brazilian pharmaceutical industries, as well as contributes to the implementation, reformulation, and improvement of Lean Six Sigma programs in this industrial segment.

Keywords: Lean manufacturing. Six sigma. Production management. Pharmaceutical industry.

INTRODUCTION

According to IQVIA (2019), the pharmaceutical sector is one of the most promising in the world. The global medicine market will reach about $1.8 trillion in 2026, including spending on vaccines against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The economic and financial results of the pharmaceutical industry turn this sector of healthcare one of the most profitable in the world. There are projections that Brazil is going to be in the top 6th global pharmaceutical market in 2026 (IQVIA, 2022).

Due to the essential nature of medicines, the pharmaceutical industry is less susceptible to economic crises (Costa, Kiss, Rodrigues, 2018). However, the sector has several management challenges: a long, costly, and uncertain process of research and development (R&D); increasing competition and complexity; lower performance in comparison to other types of industries; high number of recalls and interruptions in the supply of medicines; growing regulatory restrictions and public and government pressures to reduce drug prices. From 2002 onwards, faced with this context, the Food and Drug Administration (FDA) and other regulatory agencies began to promote deep changes in the pharmaceutical industry. Among the purposes of these changes, there

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are: encouraging the use of a more scientific perspective for the development and manufacturing of products; motivating the use of innovative production and quality assurance technologies and stimulating increased efficiency, agility, and flexibility in manufacturing. Despite the efforts of regulatory authorities, a high number of recalls and medicines shortages took place in the United States and abroad due to quality problems. Continuous improvement is part of the FDA's initiatives to optimize quality, especially of legacy products[1] (Yu, Kopcha, 2017). Lean Manufacturing (LM) and Six Sigma (SS) are the most widespread and widely used methodologies to implement continuous improvement in industries and in the service area (Cauchick-Miguel, Scheller, Sousa-Zomer, 2018; Paladini, Walter, 2019).

In operational excellence[2] programs, fundamentals of the LM and SS methodologies are integrated into the organizational culture and strategic management of companies (University of St. Gallen, 2019). According to the international benchmarking study "Operational Excellence in the Pharmaceutical Industry", compared to other types of industry, the pharmaceutical organizations are slow in adopting the principles of operational excellence (Bellm, 2015).

The LM concept emerged after the end of World War II, in the Japanese automobile industry Toyota Motors Company. It is defined as an integrated multidimensional approach that encompasses a wide variety of management practices based on the philosophy of eliminating wastes (activities that consume resources but create no value) (Antony, Hoerl, Snee, 2017). Motorola developed the SS methodology in the mid-1980s. It is a systematic approach to process improvement based on statistical techniques and scientific methods, which aims to reduce process variability and the number of defects in products and services (Patel, Patel, 2021).

The integrated use of the two methodologies, called Lean Six Sigma (LSS) is more efficient than the use of separate approaches. The two methods are compatible and complementary, so that the benefits of one methodology can offset the limitations of the other, enhancing the results achieved (Werkema, 2012; Cauchick-Miguel, Scheller, Sousa-Zomer, 2018). LSS is conceptualized as a business optimization methodology that aims to maximize shareholder profits by improving quality, speed, customer satisfaction and cost through a blend of LM and SS tools and principles (Raja Sreedharan, Raju, 2016). Recent literature reviews point to an increasing number of articles on LSS, especially from 2010-2012, indicating that it is a research topic in growth (Raja Sreedharan, Raju, 2016; Rathi, Singh, 2019). In Brazil, there is also an increase in the number of LSS publications, but there is still little empirical research on the topic (Cauchick-Miguel, Scheller, Sousa-Zomer, 2018; Paladini, Walter, 2019). Rathi, Singh (2019) listed the main benefits of the methodology in manufacturing: decreased inventory; reduced costs of low quality; increased customer satisfaction; shorten lead time[3]; reduction of defects in processes and improvement in productivity. However, there are intrinsic characteristics of pharmaceutical production processes that impact the adoption of LSS principles in totality, notably those originated from the LM philosophy, such as: small manufacturing batches, just in time (JIT)[4], physical arrangement in manufacturing cells, low stocks, fast changeovers[5], among others.

Pharmaceutical plants are process industries, which have large and fixed equipment, making it difficult to organize workstations into manufacturing cells (which favor the continuous flow, recommended by LM). Equipment is expensive, specialized and automatic, hence, companies aim to maximize return on assets. Large, inflexible equipment requires long changeovers, so traditionally, batches and production campaigns are large to increase resource utilization. Manufacturing below maximum capacity

1 Legacy products are those already registered (Agência Nacional de Vigilância Sanitária, 2022).

2 Operational excellence: consequence of practices adoption based on correct principles regarding the dimensions: culture, continuous improvement process, organizational alignment, and results. To achieve operational excellence, companies must achieve an elevated level of maturity and measurable success in all four dimensions (Basu, 2010).

3 Lead time is the time interval between the customer's order and the receipt of the product, that is, the time it takes a product to move through a process or a value stream from start to finish (Shingo, 1996).

4 JIT is a lean principle that aims to meet demand in the time required by customers with perfect quality (zero defects) and no waste. Products and services must be produced exactly when they are needed: not earlier so that they do not become inventories, nor later so that customers do not have to wait (Slack, Chambers, Johnston, 2009).

5 Changeover, also called machine change and set up: time elapsed in changing the production process of a batch until the manufacturing of the first good product of the next batch (Slack, Chambers, Johnston, 2009).

can increase resource costs. Additionally, there are cases it is unfeasible to reduce the size of the batches, as the performance of the process may be impaired. For example, in certain mixers, the minimum batch must overlap the equipment propeller, otherwise the mixing efficiency is impacted (Panwar *et al.*, 2015; Sieckmann *et al.*, 2018).

The pharmaceutical supply chain has a social role of ensuring that there will be no shortage of medicines for end consumers. Due to the impact on health, industries seek to guarantee high levels of service, and, for that, they adopt high inventories of product along the chain, which hinders the use of JIT. Additionally, there are other factors that corroborate to the maintenance of high stocks: seasonality and perishability of some raw materials; seasonal demand for some drugs; instability in receiving imported raw materials due to delays in transportation and customhouse and high variability in pharmaceutical market demand (Moktadir *et al.*, 2018). According to Tripathi, Rangarajan, Talukder (2019), even modern statistical forecasting techniques fail to provide accurate demand results for pharmaceutical products. In the JIT system, the supply of materials to the company must function as an extension of production and the establishment of a cooperative relationship between industries and suppliers is essential, which is not frequently observed in pharmaceutical plants (Garza-reyes *et al.*, 2018).

Sanitary authorities extremely regulate the pharmaceutical segment. The Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária, ANVISA) establishes Good Manufacturing Practices (GMP) guidelines as minimum requirements to follow in the manufacturing of medicines (Agência Nacional de Vigilância Sanitária, 2022). Many activities that would be considered waste in other types of industry cannot be eliminated from pharmaceutical processes, as recommended by LM because they are performed to ensure compliance with GMP, such as: identifications, records, segregations, checks and inspections. For the adoption of the continuous flow, required by LM, routines and practices of the pharmaceutical quality system (such as analysis, change controls, validations) should be planned and executed to minimize interruptions and waits in production processes as much as possible (Stratton, 2004).

All relevant activities related to drug manufacturing must be traceable and, therefore, must be registered. When errors are detected in the filling of documents, they must be corrected and depending on the criticality of the failures, they are classified as deviations that must be investigated and have their root causes analyzed. Errors imply waste as they increase the time to release the batches for sale and, consequently the lead time. Lately, companies have embraced electronic batch records, which simplify tracking and data management.

Equipment cleaning procedures used in the pharmaceutical industry are strictly established and must be validated. Depending on the residue to be removed and the limit adopted, lengthy cleaning procedures are necessary. Time and quantity of cleaning agents can be high due to the experimental character (based on trials) used to define cleaning procedures. As only after analysis it is possible to check if the volumes of cleaning agents and the times used were sufficient, excesses occur to ensure the removal of residues. Any optimization in the cleaning procedure requires revalidation.

In order to implement the improvements resulting from the LSS methodology, changes with regulatory impact may be necessary. These have an effect on the sanitary registration of medicines, being called post-registration changes, such as: modifications in process steps and parameters; batch size increase or decrease; changes in formulation; inclusion, replacement, or exclusion of equipment, among others. Depending on the change, the industry must conduct analytical tests, stability studies[6] and process validation and then wait for analysis and approval from ANVISA (Agência Nacional de Vigilância Sanitária, 2016). Depending on the regulatory impact, it is possible that the company gives up executing the improvements due to the costs and time required. According to Bellm (2015), the organizations avoid changing production processes due to time-consuming and expensive regulatory approval procedures, maintaining inefficient operations and outdated processes.

6 Stability studies: designed to test and provide evidence regarding the variation in the quality of the Active Pharmaceutical ingredient (API) or medicine as a function of time, given the influence of environmental factors variety, in addition to other factors related to the product itself, with the objective of establishing the retest period of the API or the expiry date of the API and the medicine (Agência Nacional de Vigilância Sanitária, 2019).

The singularities of the pharmaceutical manufacturing context denote obstacles to the application of LSS, as mentioned in the previous paragraphs. Despite this, the importance of the approach is recognized in this industrial segment. This study explores the use of LSS in Brazilian pharmaceutical industries, contributing to the understanding of the most used tools, the critical factors for the implementation and sustainability of the methodology and the gains and limitations of the approach in the sector.

MATERIAL AND METHODS

This work is an applied research as it generates knowledge about the practical utilization of LSS in the specific context of medicines production. It is characterized as a qualitative approach, which seeks to understand, particularly, the object of the study and is not concerned with population generalizations. Attention is focused on the meaning of the phenomenon, searching for its understanding (Minayo, 2017). It has an exploratory objective as it familiarizes the researcher with the subject in question, enabling the understanding of facts and the identification of relationships. According to the procedure, it is a field search, a strategy of study that explores in depth a specific reality (Gil, 2008).

In order to prepare the interview questions, a bibliographic review was conducted in the indexed databases SciELO, Web of Science, ScienceDirect, SCOPUS, Emerald Insight and in the official databases of the Health Ministry and ANVISA. The search terms were "Lean Six Sigma" combined with "literature review" and the publication period was 2010 - 2020. Additionally, searches were accomplished using different associations of the terms "Lean," "Six Sigma," "Lean Six Sigma," "Pharmaceutical Industry" and "Pharmaceutical Manufacturing" using Boolean operators "AND" and "OR," when applicable. In this latter case, the queries comprised the first year available in the database to 2020. In the SciELO database, the searches were carried out with the same expressions in Portuguese. The research terms were: "title," "summary" and "keywords" (except for databases that do not have the option "keywords"). Three hundred and fifty-five publications were found. After excluding the issues that presented not applicable subjects, 199 publications were evaluated to design the interview script. The most discussed topics and research questions were analyzed: benefits and limitations of the methodology; implementation methods; future trends and research gaps. Additionally, the use of LSS in the context of the pharmaceutical industries was investigated. The interview included questions derived from the authors' practical experience in the management of pharmaceutical production areas.

The project was submitted to the Research Ethics Committee (REC) of the National Institute of Infectious Diseases Evandro Chagas (Fiocruz), via Brazil Platform, together with the free and informed consent form and the research project. After the approval of the REC (consolidated opinion 4.777.775), interviews were conducted with ten professionals from different Brazilian pharmaceutical production plants that employ LSS. Of these ten organizations, one discontinued the use of SS tools, maintaining only the use of LM. Due to this differential, the participation of this company could contribute to a deepening of the research reflections. The study does not intend to measure the frequency of events or phenomena to generalize about the universe of pharmaceutical industries from the companies interviewed. However, it included quantifications of the interviewees' opinions. This approach only intended to apprehend the empirical perspective of the use of LSS in the pharmaceutical industry. Qualitative research samples are smaller than those required in quantitative studies due to unnecessary statistical representation. Qualitative sampling should encompass the set of characteristics and experiences that the researcher intends to target with his study (Minayo, 2017). As for the quantity of samples, we sought to include the selection of different profiles of pharmaceutical companies for the purposes of the research, considering nationality, types of pharmaceutical plants, different production lines, LSS implementation time and distinct aspects of the production system. Regarding the size of the organization, the intention was to encompass small, medium, and large companies, however, all companies that adopt LSS participating in the research are large, except for one medium company. This scenario is consistent with the literature review on LSS in Brazil, conducted by Paladini, Walter (2019). This study found that the majority of LSS employing companies in the

country (about 80%) are large. According to Patel, Patel (2021) this is a global reality since the implementation of LSS in small and medium-sized companies has been slow.

Ten managers from the Production or Operational Excellence area responded personally or remotely (via Microsoft Teams). The interviews were recorded, with their consent, and later the responses and all the comments were transcribed. For the analysis of data from the interviews, content analysis was used, defined as a set of communication analysis techniques that aim to obtain, through systematic and objective procedures of describing content of messages, indicators that allow the inference of knowledge related to the production/reception conditions of these messages. (Sousa, Santos, 2020).

RESULTS

The interviewees in this study are from the operational excellence area (60%) and the production department (40%).

Companies Taking Part in the Research and Respective Production Departments

The relationship between the characteristics of the organizations is seen in Table I. In this work, the respondents and their companies are indicated by the same letters.

TABLE I - Organizations characteristics

Company	Manufacturing Unit	Production Plant Type	Organization Size Classification
A	Multinational branch	Pharmaceutical with R&D. Additionally it manufactures outsourced products	Large
B	Multinational branch	Pharmaceutical with R&D. It also manufactures outsourced products	Large
C	Multinational branch	Pharmaceutical with R&D. It also manufactures generic and outsourced products	Large
D	Multinational branch	Pharmaceutical without R&D. Additionally it produces generics	Medium
E	National industry headquarter	Pharmaceutical with R&D. Additionally, it manufactures generic and outsourced products	Large
F	Multinational branch	Pharmaceutical with R&D. It also manufactures outsourced products	Large
G	National industry without branches	Pharmaceutical with R&D. Additionally it produces generics	Large
H	National industry headquarter	Pharmaceutical with R&D. It also manufactures generic and biotechnological products	Large
I	Multinational branch	Pharmaceutical without R&D	Large
J	Multinational branch	Pharmaceutical without R&D	Large

Source: prepared by the author, based on interviews (2021).

Note: classification of organization size performed by the number of employees (Sebrae, 2013).

Three national companies and seven subsidiaries of multinationals, located in Rio de Janeiro, São Paulo, Minas Gerais, and Paraná, took part in the survey. Ninety percent of the organizations were classified as large companies. Production lines are present in organizations in the following proportions: oral solids - 90%, oral liquids - 80%; semi-solids – 50% and injectables – 20%. Table II presents the characteristics of the production departments.

TABLE II - Production Departments Data

Plant	Number of Final Products Manufactured	Processing Type	Production System	JIT Use	JIT Adoption at Key Suppliers
A	More than 100	In batches	Push	No	No
B	Between 10 and 50	In batches and continuous flow	Push and pull	Partial	Yes
C	More than 100	In batches	Push	No	No
D	Between 10 and 50	In batches	Push	No	No
E	More than 100	In batches and continuous flow	Changing from push to pull	No	No
F	More than 100	In batches and continuous flow	Pull	Yes	Yes. Only at national suppliers
G	More than 100	In batches	Push and pull	Partial	No
H	More than 100	In batches and continuous flow	Push	No	No
I	More than 100	In batches and continuous flow	Push and pull	Partial	No
J	Between 10 and 50	In batches	Push and pull	Partial	No

Source: prepared by the author, based on interviews (2021).

Thirty percent of the companies in the survey manufacture between 10 and 50 products. The remaining produces more than one hundred items. Five of the ten respondents reported that the organizations for which they work adopt batch production and continuous flow, the latter being used only for liquids, semi-solids or injectables. In these cases, companies have filling lines integrated to the manufacturing equipment, so that immediately after manufacturing, the product can be filled, as well as stored for later filling. Batch processing is used on all oral solids production lines. Only company F adopts the pull and JIT system for all its products. Table II shows that 40% of companies choose to use a pull system for some products and a push system for others, so JIT is partially adopted. Only 20% of organizations have key suppliers that work with them in partnership in the JIT system.

Continuous Improvement Programs

All participating pharmaceutical plants have a department responsible for continuous improvement activities or operational excellence. They adopt a formal program dedicated to this purpose instituted and standardized by the headquarters. In the case of company G, the program was created by the only existing manufacturing plant. All companies train employees (including shop floor ones) in methods of continuous

improvement, covering LM and SS methodologies. All organizations adopt both approaches, except for company D. According to its interviewee, it used both methods, but SS was discontinued due to the complexity and long time required to achieve results. The other methodologies used in the continuous improvement programs of the organizations participating in the survey are Business Process Management (BPM)[7] and Agile Methodology[8].

Figure 1 presents the implementation time of LM and SS methodologies.

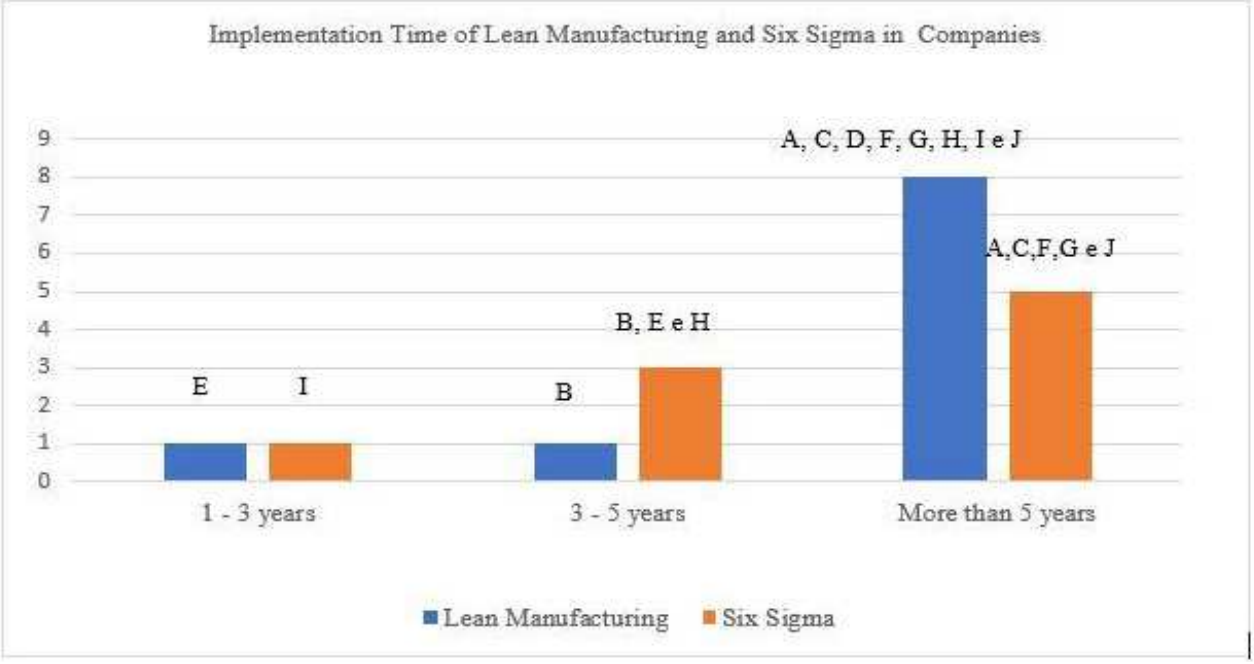


FIGURE 1 - Implementation Time of Lean Manufacturing and Six Sigma in Companies.
Source: prepared by the author, based on interviews (2021).

In the opinion of 90% of respondents, all shop floor employees or at least part of them have a culture of continuous improvement. Apart from company J, in all plants, continuous improvement actions are linked to awards or other types of financial returns. However, in some cases there is a bonus system for the best projects and in others, continuous improvement is connected to other programs, such as innovation, or to the profit-sharing goals. Interviewee J reported that the implementation of reward systems has already been considered by the company, but that encouraging competition is not a purpose of the organization.

Use of Lean Manufacturing and Six Sigma Tools in Pharmaceutical Production

Interviewees indicated the degree of use of LM and SS tools in the companies' productive areas. Figure 2 presents the results obtained.

7 BPM: comprises defining, improving and managing a company's end-to-end corporate business processes to achieve three crucial outcomes: clarity in strategic direction; alignment of company resources and greater discipline in daily operations (Slack, Chambers, Johnston, 2009).

8 Agile methodology: emerging concept in the industry that aims to achieve flexibility and fast response to changing market needs (Sindhwani, Malhotra, 2017).

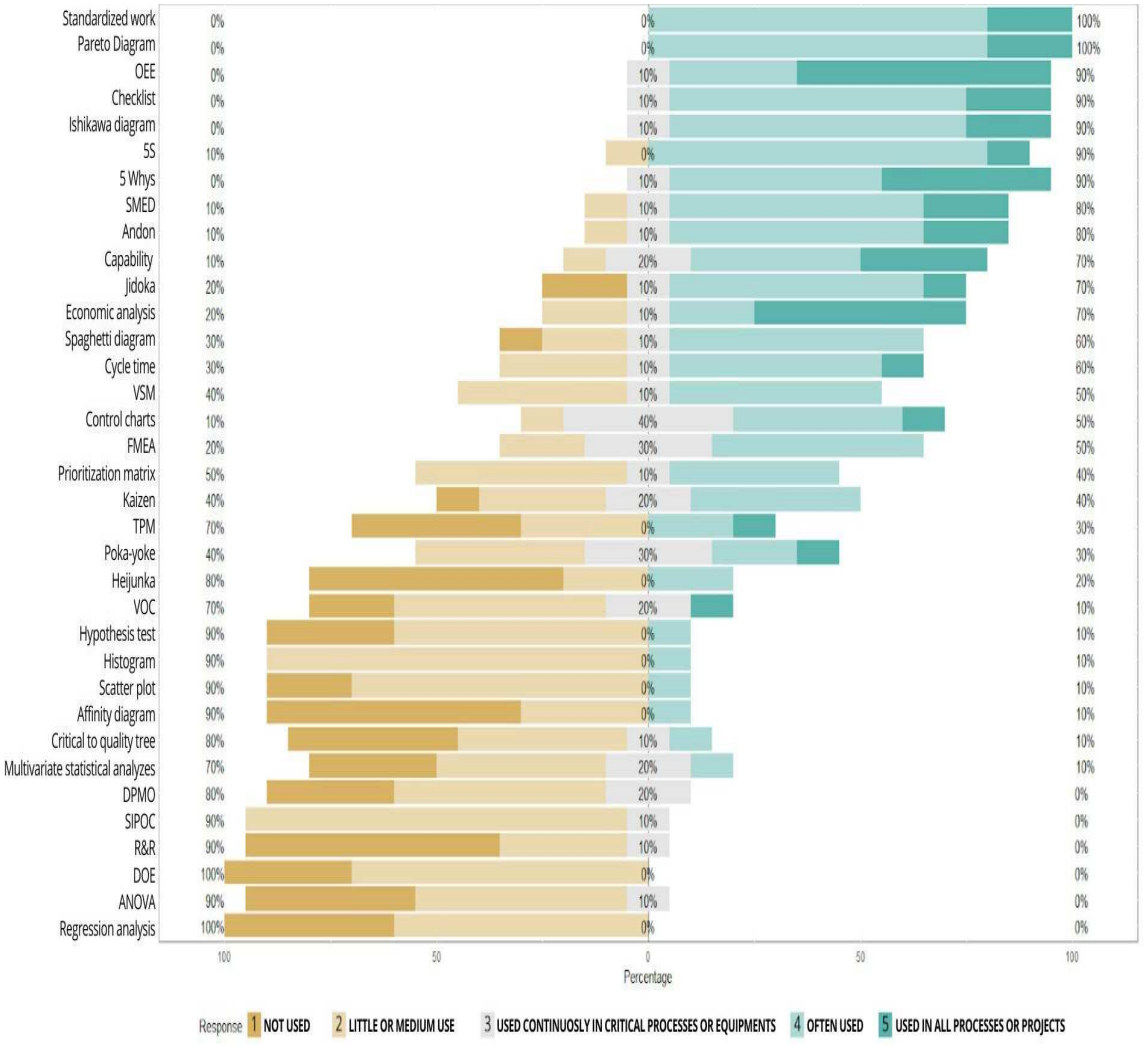


FIGURE 2 - Adoption Degree of Lean Manufacturing and Six Sigma Tools in Pharmaceutical Production.

Source: prepared by the author, based on interviews (2021).

Note: The interviewee from company J reported that Kaizen was very applied in the company, but it was replaced by Kata.

The most employed tools (with higher sums of percentages of scores 4 and 5) originated from LM: standardized work, overall equipment effectiveness (OEE), 5S, single minute exchange of dies (SMED)[9], *andon*, *jidoka*, spaghetti diagram and cycle time. Pareto diagram, checklist, Ishikawa diagram, 5 whys and economic analysis also showed high use. These tools, as well as other ones, were not developed in the LM or SS, but were included in structured approaches to build these methodologies. Some are even used in both LM and SS (Carretero, Rahim, Salah, 2010).

Control charts, failure mode and effect analysis (FMEA), prioritization matrix, value stream mapping (VSM), *kaizen* and *poka-yoke* (the last three methods originated from LM) revealed medium to high utilization. The most complex statistical techniques and other tools of SS method constituted the least used practices: regression analysis, analysis of variance (ANOVA), design of experiments (DOE), repeatability and reproducibility (R&R), defects per million opportunities (DPMO), multivariate statistical analysis, critical to quality tree, hypothesis testing. Voice of the customer (VOC), histogram, scatter plot, affinity diagram and suppliers, inputs, process, output, customers

9 SMED is a changeover reduction methodology (Shingo, 1996).

(SIPOC) also showed a low degree of use. The exceptions to the prevalence of LM tools were the reduced usage of *heijunka*[10] and total productive maintenance (TPM) and the high degree of use of capability indices, originated from SS methodology.

Respondents were asked if other LSS tools, in addition to those quoted, were used in the production of the plants. The interviewees who answered in affirmative cited the following techniques: stakeholder analysis, A3 report, *gemba* walk, *hoshin kanri*, centerlining, brainstorming, brainwriting 635, *kamishibai*, key performance indicators (KPIs) and scrum. All the tools mentioned by the interviewees belong to LSS methodology scope (Werkema, 2012) except for: brainwriting 635, which is an innovation and creativity technique and scrum, which is an agile methodology tool.

Evaluation of Lean Six Sigma Use in Pharmaceutical Production

Respondents were asked to evaluate statements about LSS. The Figure 3 shows the degree of interviewees agreement with affirmations.

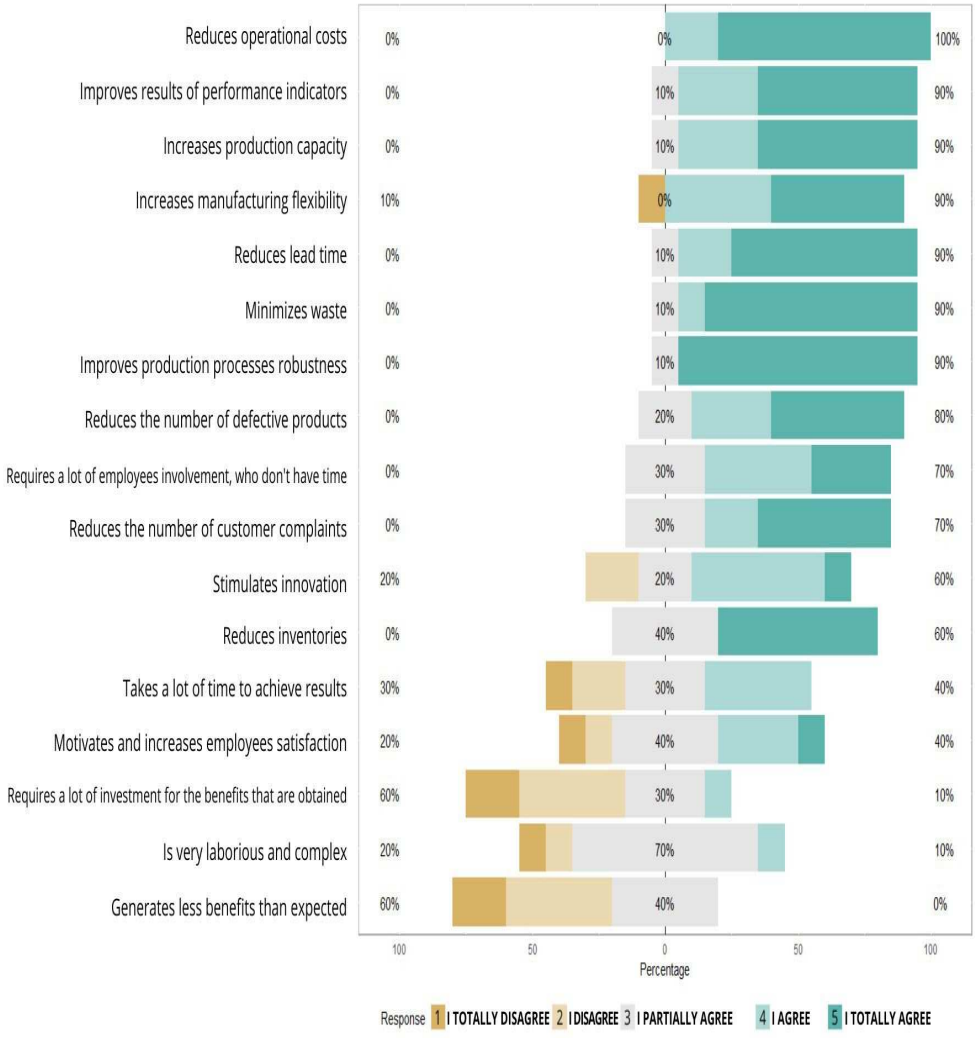


FIGURE 3 - Evaluation of Lean Six Sigma Use in Pharmaceutical Production.

Source: prepared by the author, based on interviews (2021).[10]

10 *Heijunka* is the Japanese word for leveling production planning so that the variety (mix) and volume of manufactured products are constant over a period of time (Slack, Chambers, Johnston, 2009).

The statement that obtained the highest degree of agreement (100% of scores 4 and 5) among the interviewees was that LSS methodology "reduces operational costs". The following statements reached 90% agreement: "increases production capacity"; "improves results of performance indicators"; "increases manufacturing flexibility"; "reduces lead time"; "minimizes waste" and "improves production processes robustness". Regarding the increase in manufacturing flexibility, the respondent J disagreed, commenting that in the pharmaceutical industry there are other aspects that impact the effect of LSS over flexibility, such as the fact that products are validated on previously determined equipment and changes require regulatory impact assessment. Additionally, the interviewee from company B did not fully agree with the statement and pointed out to the fact that to achieve flexibility, other aspects should be considered, such as the availability of equipment. The respondents scored with grade 5 the assertion "improves production processes robustness", except for J. He considered that a LSS project is not always able to ensure robustness to a process, and sometimes it is necessary to re-develop the product. The declarations "reduces the number of defective products" and "reduces the number of customer complaints" obtained agreement of 80% and 70%, respectively. For the statement "requires a lot of employees involvement, who don't have time", the interviewees graduated between 3 and 5. Summarizing the participants' statements, it was said that the methodology demands a lot of dedication, but if improvements are priorities for the organization, it is necessary that employees adapt their activities in order to have the time required. In relation to "stimulates innovation", respondents' opinions ranged from 2 to 5. The interviewees who disagreed with the assertion mentioned that the regulatory rigor to which the pharmaceutical industry is subjected and the excessive systematization of the LSS approach inhibit innovation. Participants who agreed with the statement reported that the approach encourages incremental innovation, especially when it is applied in the shop floor. Concerning stock reduction, the degree of agreement reached was 60%.

For the assertion "takes a lot of time to achieve results", the responses of the interviewees were divergent (ranging from 1 to 4), but there was no score 5 (I totally agree). Interviewees D and F declared that the strategy of the companies in which they work is conducting projects of small scope, but that provide quick results and that can be sequenced by other projects, promoting continuous improvement. Respondent E cited the integration with agile methodology as an alternative to accelerate results. Opinions regarding employee motivation and satisfaction were quite heterogeneous (ranging from 1 to 5). It was a statement that aroused a lot of comments, the majority mentioning that there is a disincentive at the beginning of LSS implementation, but that when participating in the program, people get motivated. Interviewees emphasized the dependence of satisfaction with recognition programs and the degree of autonomy of employees. One of the respondents reported how the company where he works encourages teams (through training, learning, and valuing the results of improvements) and highlighted that LSS improves ergonomics, which also increases people's satisfaction. It was said that if dismissals are carried out due to waste reduction (promoted by the methodology), a consequence can be demotivation.

The affirmations "requires a lot of investment for the benefits that are obtained" and "generates less benefits than expected" were the ones with the highest degree of disagreement (60%). It was reported that many results are achieved with simple tools and without a large investment of capital. Interviewees G and H cited significant gains obtained with the methodology: an increase in performance equivalent to R$ 10 million/year and the pay back of a LSS training for a team with a single project. The interviewees listed probable causes for the generation of less benefits than expected, such as: expectations created by the consultancies; inadequate estimates of the project's economic return; incorrect measurement of the benefits achieved and the existence of inefficiencies in the processes that were not detected in the initial project planning, interfering in the results. From 10 respondents, 7 scored grade 3 the statement "is very laborious and complex". Most of the interviewees considered the methodology arduous and not complex, which may explain the level of agreement obtained. Respondents also pointed out that the complexity varies with the type of project. In some cases, only simple tools

are needed and in others, more complex techniques must be employed.

Interviewees were asked about other benefits or criticisms to LSS. They mentioned the following benefits: encouraging teamwork and promoting people's engagement and the transparent deployment of continuous improvement actions up to the shop floor level. Respondents criticized the little flexibility and excessive systematization of the method. They warned that care should be taken not to use too many unnecessary tools to address the improvement opportunity, which consumes a lot of time and does not generate benefits.

Implementation and Sustainability of Lean Six Sigma Program

Interviewees analyzed the impact of certain factors on the implementation and maintenance of LSS program, using the following scale: 1 – none; 2 – low; 3 – medium; 4 – medium to high and 5- high. The factors were: dissemination of the LSS culture; project selection and management; leadership involvement; program alignment with strategic objectives; top management support and commitment; continuous training; resistance to change and innovation; adoption of a recognition and reward system; projects financial return; focus on customers and financial resources availability.

Two factors had a 90% high impact (score 5): "leadership involvement" and "top management support and commitment". One of the respondents emphasized the importance of top management presence in the projects launch, reinforcing their commitment to continuous improvement. Interviewee G spoke about the role of leadership in LSS projects focused on production bottlenecks, defined as equipment or work centers that restrict the production capacity of the entire system (Corrêa, Gianesi, 1996). Bottlenecks are critical for productivity and the support of production leaders in improvement projects aimed at eliminating them is essential for the success of these initiatives. As the dissemination of the LSS culture is a crucial factor for the methodology success, leadership engagement is essential, serving as an example for employees.

The other aspects with the greatest impact on the implementation and sustainability of the program were: "dissemination of LSS culture"; "project selection and management" and "program alignment with the strategic objectives". Based on their experiences, interviewees A and E pointed out as relevant factors for the propagation of LSS culture: the program success and the communication of projects progress and results. According to the respondents, the projects must be aligned with the deployment of the strategic objectives, which will engage people. They must be selected in a way that generates meaningful results for the organization, demonstrating the value of the continuous improvement program. It is also important that the projects are adapted to the realities of production areas. Otherwise, they end up being discontinued, leading to team frustration.

The impact of "continuous training" ranged from 3 to 5, with 80% of interviewees scoring the factor as 4 or 5. Respondent F highlighted the importance of this factor, mainly when the number of dismissals and hirings in the company is high. From those interviewed, 30% considered the impact of "resistance to change and innovation" 2 and 3 and the rest 4 and 5. Some respondents pointed out that this is a barrier that can be easily overcome whether there is top management commitment. Regarding the "adoption of a recognition and reward system", 70% of the interviewees scored 4 and 5, 20% judged 3 and 10% rated 1. It was commented that the system does not need to be financial and that the objective must be motivating and valuing work teams. Two respondents expressed difficulty in evaluating this factor due to their experiences: interviewee B measured the impact as high in function of having always worked with a recognition system and J considered the aspect without impact because he did not have this experience.

About the impact analysis of "projects financial return", the opinion of the interviewees was dissenting. Half judged the factor as 4 or 5 and the rest as 2 or 3. Respondent H declared that in the case of his organization, the Operational Excellence area aims to improve productivity and quality and therefore projects that generate gains, even if not financial, are also relevant. Interviewee J stated that invariably well-

executed projects result in financial returns. Despite the relevance of pharmaceutical products to patients, only 40% of respondents rated "focus on customers" as 4 and 5. Interviewees I and J indicated the distance between the operational area of the pharmaceutical industry and the final customer as a reason for perceiving a lower influence of "customer focus" over LSS program sustainability. In the opinion of respondent I it is more tangible to link the program to process improvement, which will influence customer satisfaction. The "financial resources availability" was the only factor that did not receive a score 4 or 5. Among the comments, it is highlighted those of interviewees G and J. Respondent G stated that after investing in training, not many resources are needed to get results. Interviewee J pointed out that currently there is a lot of knowledge about LSS methodology available, which minimizes the need to spend resources hiring external services for the program implementation and maintenance.

Respondents were asked to mention other factors that positively or negatively affect the implementation and maintenance of LSS program. They cited:

- Positive aspects: hiring a consultancy to support LSS implementation; the institution of a department responsible for improvement projects; proper selection of tools; alignment of projects with the areas of safety, environment, quality and people development, so that the adoption of improvements does not impact the precepts and objectives of these sectors; flexibility to design the program according to the company's needs, without having to follow standardized models established by consulting firms. Another positive factor mentioned was the division of a large project into smaller projects. This is a recommendation of Werkema (2012). According to the author, a frequent mistake is the establishment of a single LSS project for an overly complex problem.

- Negative aspects: changes in the direction of continuous improvement strategies adopted in the company, due to the replacement of managers (for example), which can demotivate employees; LSS culture corruption with the introduction of concepts that contradict the fundamentals of the approach.

Technologies that Enable Lean Six Sigma Use in Pharmaceutical Production

Respondents were asked to assess whether "electronic batch records" and software responsible for "shop floor automatic data collection" and "performance indicator automatic calculations" facilitate the LSS use in pharmaceutical production, employing the following grading: 1 – I totally disagree; 2 – I disagree; 3 – I partially agree; 4 - I agree and 5 - I totally agree.

The interviewees consented in high degree that the three technologies are enablers of LSS use. "Electronic batch records" obtained the lowest rate of agreement (80% of responses 4 and 5). Respondent I stated that batch documentation is not much used in LSS projects for data collection and analysis. Interviewees called attention for some precautions regarding automatic data collection systems: before implementation, it is necessary evaluating costs, integration with other systems and the existence of qualified personnel for use; it is only worthwhile analyzing the data that really have a connection with the problem and it is important ensuring that the manual entries required by automatic systems are carried out with quality and reliability. Respondent E stated that automatic collection systems allow operators time to develop more elaborate functions. It was recommended to use manual data collection before automatic systems for training and dissemination of culture and interviewee J stressed the importance of observation in the "*gemba*"[11] despite the advantages that the technologies offer.

Respondents cited other technologies or practices that facilitate the LSS use: Enterprise Resource Planning System (ERP); software: statistical data analysis, such as Minitab, project management, Laboratory Information Management System (LIMS) and process mapping; Power BI; E-learning (in some cases, the operators themselves provide training); RFID for inventory monitoring, for example; QR Code; virtual reality and augmented reality (the latter two have been used in training to show operators machine details). Respondent A mentioned that he believes the artificial intelligence use will greatly contribute to LSS.

11 *Gemba* is a Japanese word meaning the "true place". Going to the *gemba* is going to the factory floor to observe the facts, understand the problems and identify opportunities for improvement (Werkema, 2012).

Factors that Hinder Better Results of Lean Six Sigma in Pharmaceutical Manufacturing

The difficulty imposed by certain factors to LSS use in pharmaceutical manufacturing was evaluated according to the scale: 1 – totally disagree; 2 – I disagree; 3 – I partially agree; 4 - I agree and 5 - I totally agree. The factors were: GMP compliance activities; regulatory impact of improvements; difficulty of changes in the production flow; large production batches and campaigns; high variability in demand and strict and validated cleaning processes.

The factor "GMP compliance activities" showed 100% agreement (sum of scores 4 and 5). These activities, essential for pharmaceutical operations, consume time and cause interruptions in production processes, impacting the gains that LSS could provide. The factors "regulatory impact of improvements" and "difficulty of changes in the production flow" obtained 90% of responses 4 and 5. Regarding the first factor, interviewees D and I alerted to the possibility of seeking more flexibility with ANVISA, presenting risk analyses and impacts of changes. Respondents mentioned that the "difficulty of changes in the production flow" includes the classification of manufacturing areas (in the case of sterile products) and post-registration changes related to equipment. Interviewee E stated that pharmaceutical plants projects should consider the continuous flow of products due to the difficulty of later modifications.

Two factors showed 80% of agreement: "large production batches and campaigns" and "high variability in demand". In the case of the first factor, only interviewee F (from the company that adopts the pull system and JIT for all products) disagreed that this impacts the achievement of better results in pharmaceutical industries. According to this respondent's comment, the company seeks to reduce batch sizes as much as possible, being limiting factors: the capacity of the equipment and the registration of the products. For batch size changes, the company must follow the specific rule for post-registration changes (Agência Nacional de Vigilância Sanitária, 2016). Respondent E pointed out the importance of using SMED to enable batch size reduction. As highlighted by interviewee J, the growth of markets that require more specialized drugs will require smaller batches. In relation to "high variability of demand", respondent F (who uses a pull system and JIT for all products) reported his experience with stable demands, citing that instability occurs only at the end of the months due to increased sales. At these moments, the company decides whether to make stock or overtime to satisfy demand. In contrast, interviewee H has experienced great uncertainty in demand, as the industry mostly deals with volumes of public bids. He pointed out as difficulties in adopting JIT: the lack of accuracy in sales forecasting and the wide variety of items. Respondent E reported that he believed that demand fluctuations are more critical obstacles to JIT than the large mix since the high variety of products was a characteristic of Toyota's production system. Interviewee J cited the Brazilian dependence on imported pharmaceutical raw materials as another difficulty in implementing JIT due to the need to generate inventories to overcome logistical obstacles.

The factor that presented the lowest degree of agreement was "strict and validated cleaning processes" (60% of scores 4 and 5). Respondents commented that drastic changeover reductions (such as those reported in the automotive sectors) are not obtained, but significant optimizations in set up times are achieved in pharmaceutical plants, despite the strict degree of cleaning requirement.

Interviewees indicated other factors that hinder LSS use in pharmaceutical production. It was mentioned that the methodology does not reach the magnitude that it presents in other industrial sectors because the financial returns of some LSS projects are insignificant compared to the high profit margins of the pharmaceutical industry. Corroborating this statement, respondent F cited as an unfavorable element the culture that the pharmaceutical industry has of disregarding small results. The lack of partnerships with suppliers was also pointed out.

Relevance of Lean Six Sigma Tools

Respondents indicated the LSS importance for certain aspects, according to the scale: 1 – low; 2 – low to medium; 3 – average; 4 - medium to high and 5 - high. The aspects were: "culture of continuous

improvement"; "productivity optimization"; "achievement of the organization's strategic objectives"; "obtaining competitive advantage"; "quality improvement"; "increased financial gains"; "safety and environment"; "development of work teams" and "customer satisfaction".

The factors for which LSS is most relevant (100% of grades 4 and 5) are: "culture of continuous improvement", "productivity optimization" and "achievement of the organization's strategic objectives". Regarding these aspects, the interviewees considered that the continued use of LSS generates the incorporation of continuous improvement to the company's culture; that the approach promotes the optimization of plant productivity, despite the unique characteristics of the pharmaceutical industries and that the methodology is not applied in its entirety, which impacts its importance for the achievement of strategic objectives. The value of LSS for "obtaining competitive advantage" reached 90%. LSS allows the company gaining competitive advantage by adding value to products, reducing costs, assimilating the culture of "overcoming obstacles" and speeding up delivery.

For the items "quality improvement" and "increased financial gains", the methodology presented 70% of scores 4 and 5 and 30% of value 3. Once again, it was expected that the relevance of LSS for quality improvement would be higher when compared to the other factors evaluated. Respondent J reported that despite the company has been using LSS for more than 10 years, the quality department works much more in "policing" than in consolidating quality in production. As for "increased financial gains", one of the interviewees stated that the methodology does not always promote increased gains, but invariably reduces costs.

The importance of LSS for "safety and the environment" was rated 4 and 5 by 60% of respondents. The relevance of the approach to the environment was highlighted due to the focus on reduction of waste. However, there were respondents who reported that LSS projects aimed at environmental management are still not widely carried out in pharmaceutical companies. Respondent I opined that the lower value of the methodology for this item is due to the fact that the pharmaceutical industry already adheres to safety standards and has low environmental impacts, when compared to other types of industrial segments. The LSS value for the "development of work teams" ranged from 2 to 5, with 20% scoring 2 and 60% scoring 4 and 5. One of the research participants reported that although LM exerts an influence on the construction of mentality of individuals, there are many other elements that influence the development of teams. For "customer satisfaction", the relevance of LSS presented 60% of value 3, 10% of score 2 and the rest of answers 4 and 5. One possibility to explain this result expressed by the interviewee G is the belief that as the pharmaceutical industry adopts many controls, it already ensures the quality of products delivered to customers. Thus, LSS would not have much to contribute to customer satisfaction.

DISCUSSION

This study sought to investigate the characteristics of LSS employment in the pharmaceutical production of plants that took part in the interview and correlating these characteristics with the specificities of this industrial segment. Additionally, it aimed to discriminate the gains that the methodology brings to the pharmaceutical industries, especially for continuous improvement actions, which have been encouraged by regulatory agencies.

The companies' profile was explored. Oral solids production lines are present in 90% of the plants. Batch production is the type of processing used in these lines, being in coherence with the literature which states that the standard for oral solids manufacturing in the pharmaceutical industry is batch processing (Vanhoorne, Vervaet, 2020). Regulatory authorities, including the FDA, have been encouraging industries to adopt continuous manufacturing as they recognize that this technology has the potential to improve product quality. Currently, however, there are still many barriers to the continuous manufacturing implementation (Vanhoorne, Vervaet, 2020). Despite employing LSS, not all organizations use pull system and JIT or do not apply them in their entirety. In fact, only F company uses a pull system for all its products and employs JIT, including in its key national suppliers. This organization manufactures over 100 final products. Although JIT approach is more difficult to apply in companies with

a large mix (Corrêa, Gianesi, 1996), in pharmaceutical industries, the great variety of products does not appear to be a significant constraint for JIT. The benchmarking conducted by University of St. Gallen (2019) indicated that industries with the best scores on JIT adoption degree manufacture a large mix of products. In all organizations, continuous improvement or operational excellence is coordinated by departments dedicated exclusively to these activities, which include the training of shop floor personnel. Employee involvement is a capability that supports continuous improvement (Gonzalez, Martins, 2016). It is also a principle of LM, operationalized by the practice of autonomy, which consists of delegating increasing responsibilities to shop floor employees, as stopping processes in case of problems (Slack, Chambers, Johnston, 2009). A recognition and reward framework, pointed out in the literature as one of the critical factors for the implementation and sustainability of LSS methodology (Patel, Patel, 2021), was revealed as a significant aspect in the group of pharmaceutical companies studied, since 90% of these use some kind of recognition system.

The work shows a greater use of LM tools in pharmaceutical production, compared to SS. A probable cause to explain this predominance is the fact that LM is simpler and easier to understand and implement. SS projects are time-consuming (Carretero, Rahim, Salah, 2010). According to Antony, Hoerl, Snee (2017), if the solution to the problem is known, the principles of LM are suitable for resolution, being unnecessary extensive collection and analysis of data, demanded in SS. On the other hand, when the solution to the problem is completely unknown, long-term SS projects are more likely to be required. The scopes of LM are the continuous flow of products and information and system efficiency, while the focuses of SS are defect reduction, statistical control, stability, precision, and effectiveness of processes (Carretero, Rahim, Salah, 2010). Another hypothesis for the lower adoption of SS is that, due to its objectives, it more frequently requires post-registration changes, which may discourage its use. The time and cost of these changes can hinder the SS improvement initiative.

Despite *heyjunka* and TPM being LM tools, they showed reduced usage. *Heijunka* is a premise for using JIT. As seen earlier, JIT is adopted in only one corporation and partially applied in 4 companies, which justifies the low use of *heijunka*. TPM is a methodology based on 8 pillars, which are not always implemented by all organizations (Bhatti, Jain, Singh, 2014). Among the respondents of this research, those who work in organizations D and G commented that they predominantly use the autonomous maintenance pillar, defined as encouraging the autonomy of operators, so that they assume the simplest maintenance activities: cleaning, lubrication, inspection, and adjustment equipment (Bhatti, Jain, Singh, 2014). One hypothesis for the interviewees to have pointed out a reduced degree of TPM use is the non-integral employment of methodology. Capability indices, despite being SS tools, revealed high use, probably due to the fact that they are recommended for evaluating trends in the Periodic Product Review[12], a mandatory quality tool for compliance with GMP standards (Agência Nacional de Vigilância Sanitária, 2018).

In the interviewees' evaluation of LSS adoption in pharmaceutical production, the statements that the approach "increases manufacturing flexibility" and "improves production processes robustness" obtained a high degree of agreement. However, it was highlighted that flexibility in the pharmaceutical industry is affected by regulatory aspects. In fact, after a process validation, the inclusion, replacement or exclusion of an equipment from a medicine`s production flow is a post-registration change, requiring regulatory impact assessment (Agência Nacional de Vigilância Sanitária, 2016). The same interviewee commented that LSS does not always improve processes robustness because sometimes the products have to be redeveloped. LSS is not suitable for process redesign. In this case, it is pertinent to use Design for Six Sigma (Werkema, 2012). As the reduction of defective products and process variability is an objective of LSS, it was expected that in the interviewee's opinion, the methodology would be more relevant for quality improvement, especially when compared to other judgments made by the respondents. A possible cause may be the lower degree of SS use

12 Periodic Product Review is a quality tool that helps in the identification of corrective and preventive measures related to the integrity of the product, process, and its controls, favoring continuous improvement (Agência Nacional de Vigilância Sanitária, 2018).

compared to LM. Another hypothesis is originated from the observation that the quality processes of the pharmaceutical industry are oriented to ensure that defective products are not shipped from the company but are not focused on improving the inherent quality of manufacturing processes. Usually, companies incur in quality improvement costs (with narrower specifications and more inspections and production controls, among others) and are not necessarily successful in reducing the intrinsic failure rate of processes (Basu, 2010). Therefore, it is likely that LSS projects are not being directed towards effective quality improvement.

While respondents were evaluating the statement "LSS stimulates innovation", some of them highlighted incremental innovation on the shop floor. The connection between LSS and incremental innovation is addressed in literature. Antony, Hoerl, Snee (2017) reported the results of a study which demonstrated that firms adopting LSS initiatives experience a positive effect of LSS on incremental innovation and innovation capability. One of the most accepted benefits of LM is the reduction of inventories and therefore a greater recognition of this gain in the pharmaceutical manufacturing was expected. A possible reason is the reduced or partial adoption of JIT and pull system in the companies, as seen in Table II. If all the principles of LM were used according to their original designs, the reduction of inventories in the pharmaceutical industry could be greater.

Respondents' opinion on the time needed to achieve LSS results was diverse. The time to obtain the results depends on the project, the methodology and the tools used, which explains the divergence in the evaluations. The respondent who works at plant D (which discontinued SS) agreed that SS takes a long time to produce results, but LM does not. This statement based on the practical experience of the interviewee is in line with what is described in the literature (Carretero, Rahim, Salah, 2010). Most respondents disagreed that a large availability of financial resources is necessary to obtain LSS benefits. Furthermore, this factor was not considered of high impact on the implementation and sustainability of LSS program. These results encourage the adoption of the methodology in public administration and in small and medium-sized companies, which have more restricted budgets.

Compared to other aspects, "customer focus" had a low impact on LSS implementation and maintenance. Additionally, the relevance of LSS to customer satisfaction was expected to be greater. SS tools are very focused on customer satisfaction (Patel, Patel, 2021) and their lesser use (compared to lean techniques) can explain these results. Another hypothesis pointed out by the respondents was the lack of perception of end customers' needs due to the distance between them and pharmaceutical production. One interviewee assumed that LSS would not have much to contribute to customer satisfaction because the pharmaceutical industry is very committed to ensuring the quality of medicines delivered to patients. However, it should be remembered that "customer satisfaction" does not encompass only quality, but involves other factors, such as cost, which can be reduced with the adoption of LSS approach.

The methodology was not considered as relevant to "safety and the environment" as it was to other factors. One of the causes may be the reduced number of projects with this focus in the pharmaceutical industry. The research about integration of LSS and other themes, such as environment, life cycle assessment, sustainability and energy management is recent. The lack of top management commitment; training and education and investment for environmental projects were identified as barriers to the implementation of LSS integrated with sustainability (Paladini, Walter, 2019; Patel, Patel, 2021).

Among the technologies that ease LSS employment, "electronic batch records" had the lowest degree of agreement in the opinion of respondents. However, "electronic batch records" reduces the documentation filling errors, increasing the right first time (RFT), an indicator that measures the ability to obtain the intended performance the first time the process is executed. The concept of RFT is aligned with LM. Whenever an activity is performed the first time without errors, resources will not be wasted on rework, delays, product discards, deviations, overtime, among others (University of St. Gallen, 2019). Artificial intelligence was indicated as a technology that enables LSS use. In fact, literature presents as a future trend the integration of LSS with data science technologies such as big data, the internet of things and artificial intelligence (Antony, Hoerl, Snee,

2017; Gupta, Modgil, Gunasekaran, 2020). FDA has also been encouraging both continuous improvement and advanced manufacturing technologies, such as 3D printing and high technology and computer-controlled production facilities (Arden *et al.*, 2021).

The interviews revealed the factors that hinder better LSS results in the pharmaceutical industry: activities that ensure compliance with GMP standards, the regulatory requirements for implementing improvements and the difficulties for changing production flows. Depending on the regulatory impact of changes required by improvements, time and cost can be high, hampering processes optimization. The "difficulty of changes in the production flow" encompass not only the use of large and fixed equipment, but also include regulatory aspects, as pointed out by respondents. In order to turn the production flow more continuous, it may be necessary to include, replace or exclude equipment, which configures a post-registration change. Additionally, in the case of sterile products, manufacturing must be carried out in clean areas. These are classified in grades A, B, C or D depending on the concentration of particles in the air and the operations that can be conducted in each area. For example, sterile pckaging must be carried out in a grade A clean area (Agência Nacional de Vigilância Sanitária, 2022). Therefore, to execute an operation in other location, this must be properly classified. Even if the plant construction project already considers continuous production (as pointed out by an interviewee), there may be a need to change the layout due to new products, equipments or technologies.

In the opinion of respondents, the aspects "large production batches and campaigns" and "high variability in demand" also have a high impact on LSS gains. Companies tend to opt for bigger batches so that the production costs are divided by a larger quantity of items, reducing the cost per unit produced (Corrêa, Gianesi, 1996). The longer the downtime of the production line due to the changeover, the higher the costs. Reducing set up time through SMED makes batch sizes reduction possible. Small batch processing will also be required by the growth of personalized medicine[13] and special medicines[14] markets (Ross, 2020). Instability in demand is recognized as an element that hinders the implementation of LM. According to Corrêa, Gianesi (1996), it is more difficult to apply the JIT system in plants that have a high variety of products and unstable demand. The Brazilian dependence on imported pharmaceutical raw materials was pointed out as an adversity to JIT because it presumes greater logistical challenges. It becomes more arduous manufacturing products exactly when they are requested by customers. In July 2022 the growth in imports of APIs was 23% compared to the pandemic period and 59% compared to the average of the previous five years. In this period, Brazil was importing 95% of the APIs used in the national production of medicines (Datamarnews, 2022). The factors that impact LSS gains in the pharmaceutical industry combined with the predominance of LM tools over SS ones and the fact that methodologies are not always employed according to their original conceptions contribute to the operational excellence gap between the pharmaceutical industry and other manufacturing segments.

CONCLUSION

This study corroborates to the relevance and pertinence of the pharmaceutical industry to the health system as it contributes to the continuous improvement of the products supplied to the Brazilian population.

Despite the pharmaceutical industry specific characteristics, which impact the potential gains of LSS, many benefits are observed in production plants, such as: operating costs reduction, performance indicators optimization, production capacity increase, waste minimization, processes robustness improvement, among others. LSS has a great value in the pharmaceutical industrial segment. Most companies that participated in the survey have been using LM and SS methods for more than three years and 50% of them for more than five years. These data demonstrate that pharmaceutical industries that employ LSS recognize its relevance.

13 Personalized medicine: medicine field that employs diagnostic tests to determine which medications and dosages work best for a patient (Ross, 2020).

14 Special medicines: there is no single definition for special medicines, but there is a consensus that they are expensive, difficult to administer, require special treatment or ongoing clinical evaluation (Lotvin *et al.*, 2014).

This work contributes to empirical research on LSS in Brazil. According to the literature, there are few studies of this type on the subject. The interview script elaborated can be used or adapted for other research in pharmaceutical plants or in other industrial sectors. The knowledge gained from this work corroborates to the implementation, reformulation and improvement of LSS programs in the pharmaceutical industries.

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