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LEAN MANAGEMENT APPLICATION IN A LOPERAMIDE HCl-ORODISPERSIBLE TABLETS (HCl-ODT) MANUFACTURING LINE

Abstract: *The Lean Management had its origin in the 50s in the Japanese automobile industry, and is currently used in different production processes, included those related to pharmaceutical production, for which has raised its application in the manufacture of loperamide HCl-orodispersible tablets (HCl-ODT) under the coordination of the Pharmaceutical Quality System (PQS). A theoretical proposal for process reengineering has been carried out both incorporating and applying the different Lean tools in the industrial manufacturing process of HCl-ODT, and their subsequent integration into the PQS, through each one of the processes stages, such as: weighing, screening, mixing, compression, and packaging, under the compliance of the current legislation of the pharmaceutical industry and in compatibility with what is established in the ICHs within the Quality System, in order to increase the effectiveness and efficiency of the process and its profitability. Lean Management under the coordination of the Pharmaceutical Quality System (PQS), is an excellent strategy for manufacturing loperamide HCl-orodispersible tablets since it improves its Quality System, as well as facilitates compliance with the national and international guides, standards and legislation that are suitable to it.*

Keywords: *Lean Management, management tools, pharmaceutical management, pharmaceutical quality system, industrial pharmaceutical manufacturing, loperamide HCl-orodispersible tablets.*

1. Introduction

The concept of "quality" presents a wide range of definitions depending on the prism through which it is observed. In the field of business management, several methodologies have been incorporated from the end of the 19th century to the present. All of them not only contribute to the implementation and maintenance of a Quality Management System, but also are aligned and coordinated under the fulfillment of national and international legislations that are suitable throughout the drug's life cycle. Some of those regulations are: ICH (International Conference on Harmonization), GLP (Good Laboratory Practice), GCP (Good Clinical Practice), GMP (Good Manufacturing Practice), GDP (Good Distribution Practice), GRP (Good Regulatory Practice), GVP (Good Pharmacovigilance Practice), CREC

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(Clinical Research Ethics Committee) and GPP (Good Pharmacy Practice). Their common aim is to obtain proven quality, as well as safety and efficacy in every process (Camisón, 2006; Roncales, 2014).

At the beginning of the 20th century, the pharmaceutical industry was far from being the reflection of the current one. In its beginnings, 1906, the FDA (Food and Drug Administration) in the USA banned food and medicines misleading and adulterated labels. It should be noted that during this period the Pharmacopoeias and the National Formulary established a series of official standards such as the quality and purity of the active ingredients. Nevertheless, the lack of safety in marketed drugs caused noteworthy a series of fatalities, as the poisoning of patients due to the administration of the sulfanilamide elixir with diethylene glycol, occurred in 1936, or the side effects caused by thalidomide in the year 1960, which evidenced the need to improve the safety of marketed medicines.

This is how, hand in hand with the FDA, it came the first edition of the GMP regulation in 1963. Within this framework, in 1967, during the XX World Health Assembly, the WHO (World Health Organization) was requested to stablish the GMP and a Quality Control to guarantee the suitability of medicines, being mandatory in the European Union since 1992 (U.S. FDA, 2004; Montoya & Salazar, 2007; Arayne et al, 2008; Jain & Jain, 2017).

The incorporation of process validations in the GMP became a fundamental milestone for the assurance of the quality, safety and efficacy of medicines. In 1991 the ICHs was created with the purpose of harmonizing common requirements from the main powers of that time (USA, Europe and Japan) thanks to the Sinergy between industry and administration. The so-called observers generate a series of recommendations, some of them worldwide accepted today and being part of the current regulations, among which are the ICH Q9 (Quality Risk Management) and ICH Q10 (Pharmaceutical Quality System) (Salazar & Roquet, 2005).

In the 21st century there is a qualitative leap in quality, a clear example of which is the publication of the FDA's final report entitled "Pharmaceutical CGMP for the 21st Century. A risk-based approach final report". It is the first reference of a modern quality system which is global, robust and in accordance with the GMP with regard to its guiding principles, and at the same time to a risk-based orientation, science-based policies and standards, oriented towards integrated quality systems, international cooperation and strong protection of public health (Salazar & Roquet, 2005; U.S. FDA, 2021; ICH).

At this point, the state of the art requires a method to be applied to the reengineering of pharmaceutical manufacturing processes, in which the benefits of using Lean tools in coordination with its current quality system are analyzed. This study presents a theoretical approach on how to use the tools of the LEAN methodology for the manufacture of loperamide HCl orodispersible tablets (HCl-ODT) under the coordination of the Pharmaceutical Quality System (PQS).

Subsequent studies should be carried out using the proposed method for the manufacture of loperamide HCl orodispersible tablets (HCl-ODT) under the coordination of the Pharmaceutical Quality System (PQS) as a model for its use in the different pharmaceutical production lines.

1.1. Pharmaceutical Quality System (PQS)

In the Chapter 1 of the GMP Guide for Medicines for Human and Veterinary Use is contained the minimum requirements and needs to establish, monitor and improve a PQS. It justifies each and every one of the activities that are part of it and established:

"*The holder of a Manufacturing Authorization must manufacture medicinal*

products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization or Clinical Trial Authorization, as appropriate and do not place patients at risk due to inadequate safety, quality or efficacy" (Agencia Española de Medicamentos y Productos Sanitarios, 2012).

The requirements that guarantee the PQS can be summarized in the following (Agencia Española de medicamentos y productos sanitarios, 2012):

- PQS suitable design: Defined and documented, Quality manual or equivalent document, description of the Quality Management system, responsibilities of the management.
- Operational, support and strategic actions around GMP: Design and development of the drug according to GMP. Guarantee the correct manufacture, supply, use of starting materials and packaging materials and the selection and verification or monitoring that each delivery comes from the approved supply chain. Description of production and control operations according to GMP. Need for controls on intermediate products and in-process controls and validations. Development and use of effective systems for monitoring and control of processes and product quality. Procedures that ensure the management of subcontracted activities. Storage, distribution and handling of medicines in such a way that the quality remains intact during its the validity period.
- Finished product release: Batch liberation, deviations investigation and the decision of preventive actions to avoid them require from the results of product and process monitoring. Uniform release of drugs with appropriate quality attributes. Certification by a qualified person of each manufacturing batch.
- Knowledge management: Management of the characteristics and properties of the product and processes in all stages of the product's life
- Change management: Existence of measures implemented for the prospective evaluation of planned changes and the approval prior to their implementation, also considering the notification and subsequent approval by the regulatory authorities when necessary. Assessment to confirm that quality objectives have been achieved and that there have been no unintended negative impacts on product quality following the inclusion of any changes.
- Deviations, suspected product defects or other types of problems must be addressed in accordance with quality risk management.
- Continual improvement: implementation of quality improvements appropriate to the current level of knowledge of the process and product.
- PQS assurance: Procedure of self-inspection and/or quality audits, so with its application the PQS effectiveness and application is regularly evaluated.

Planning, implementation, monitoring, and continuous improvement of the PQS must guarantee the generation of value, where the quality, safety and efficacy of the medicines are collected according to the link in the life cycle of it, such as its production processes or quality controls and in general terms, a management system has to conform to the set of interrelated elements.

In order to generate value for the interested parties (internal and external clients) the processes and work methods must be made up of a set of activities that present some

inputs and outputs to the next process. It requires a series of material resources and personnel, to be able to carry out the processes and to maintain the management system (Calso & Pardo, 2018).

ICH Q10 guide, included in Part III of the GMP is a complement to Chapter 1 and refers to a PQS understood as a "*Management system to direct and control a pharmaceutical company with regard to quality*". In addition, the International Organization for Standardization (ISO), publishes a series of international standards covering almost all industries, that constitute a set of requirements that any organization can voluntarily comply. In the case of ICH Q10 Guide, it includes an approach reflected in the UNE ISO 9,000 series, which constitutes a series of standards and guides on quality and its management system. It is intended to standardize the quality of the products and services offered by a certain entity or organization, such as the pharmaceutical industry. The PQS is based on the concepts of quality of the ISO Standards, on the implementation of the GMP and on the application of different guides, such as: ICH Q8 (*Pharmaceutical development*), ICH Q9 and ICH Q10 (European Medicines Agency, 2015; ISO, 2015; EALDE business school, 2020).

The pharmaceutical laboratory must establish its own identity, that is, its mission, the image of the future it wishes to achieve or vision and the fundamental principles by which it is governed that are its values. All members of the organization should know mission, vision and values.

Continuous improvement must be considered as one of the fundamental parts of the PQS. Its implementation covers the whole drug cycle in accordance with the established purposes. The identification of its capabilities carried out through a PQS must ensure the expected results, an increase in the desirable effects, in order to generate value and provide improvements by evaluating the risks and opportunities (Blasco et al, 2018).

1.2. Lean Management applied in industrial pharmaceutical manufacturing processes

Lean Management has its origins in the 1950s in the Japanese automobile industry with the beginnings of what became popularly known decades later as the Toyota Production System (Cabrera, 2012; Gil, 2017). A series of conditions led to the birth of this new methodology and work system, as well as its adaptation to change. The extreme crisis that the Japanese country suffered during the decades after the World War II (1939-1945) together with the insufficiency of raw materials, among other factors, promoted the application of this methodology in coordination with other existing models, such as those previously formulated by Deming and Juran.

The Korean War (1950-1953) boosted the market for military vehicles at the request of the US army and all this motivated the development of a series of tools that use this management philosophy. In the 1970s it was possible to structure a standardized work system, with the influence of Western Quality Management, in such a way that the deployment of the system to other industries, among them the sanitary one, took place between 1995 and 2005. The Technological Institute of Massachusetts, by studying, adapting and disseminating the keys to the Japanese production system, made this new management philosophy known to the world. It is applicable to any business and industrial field, and which today is known under different terminologies such as Lean, Lean Manufacturing, agile manufacturing, flexible manufacturing, just-in-time or synchronous manufacturing, continuous flow manufacturing, world-class manufacturing or the Toyota Production System.

The adversities that motivated the creation and development of Lean, were based on the simplicity of the value chain. Its focus is on the client or interested parties, which

together with the human factor constitutes a fundamental part. The use of a series of tools (Lean Tools), that conveniently focused within an organized structure, manage to adapt to a PQS, is at the same time compatible with other methodologies aimed at reducing variability, such as Six Sigma (Iglesias, 2017).

The economic crisis of the first decade of the 21st century also led to a series of changes in the pharmaceutical industry. Appeared concepts as cost containment measures, improvements in its management and manufacturing systems, while guaranteeing the implementation and harmonization of the quality required by the health authorities and in addition to the factors exposed. Others related to global competition, customer demand and continuous technological development must be added, which made it necessary to adapt to the circumstances, being a possible solution, the application of a management system based on the Lean Management (Vogler et al., 2011; Pramadona & Adhiutama, 2013; Nenni et al., 2014; Torre et al., 2023; Rahardjo et al., 2023).

In a practical way, the application of the Lean Management contributes to the maintenance and improvement of the PQS, since it is capable of adapting thanks to a series of characteristics they both share in common, such as the focus on the client, the search for simplicity in processes, effectiveness and efficiency or continual improvement.

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1.3. Hypothesis and objectives

The proposed hypothesis is the following: Since Lean Management is widely used to improve production processes; and it has proven to be an effective and adaptable tool, it should contribute to facilitating the comprehensive management of drug manufacturing under the strictest quality standards.

The general objective was to make a theoretical proposal for the use of Lean tools at each of the stages of the manufacturing process of loperamide hydrochloride orodispersible tablets (HCl-ODT) under the high-quality standards of pharmaceutical production in compliance with the requirements set forth in current legislation. As a specific objective, a proposal for the use of Lean tools was deployed in the industrial scaling of said pharmaceutical formulation, as well as its coordination with the implemented quality system.

2. Material and methods

2.1. Material

Lean Tools used have been the following (Figure 1):

- Value Stream Mapping*:* It allows all planning and manufacturing activities to be identified, in order to find improvement opportunities that have an impact on the entire production chain and not only on isolated processes.
- 5S: Its objective is to keep the facilities in a state of review, which is achieved through the following five basic principles: Seiri *(Eliminate everything necessary)*, Siton *(Order everything necessary)*, Seiso *(Clean and inspect the environment to identify Fuguai (defects))*, Seiketsu *(Standardize to consolidate the goals achieved in the application of the first "S")*, Shitsuke *(Normalize self-control).*
- SMED *(Single Minute Exchange of Die):* It is based on a reduction in preparation times, thereby allowing

work with smaller batches, that is, shorter manufacturing times, which will have an impact on improving delivery times and product levels in transit.

- TPM *(Total Productive Maintenance)*: It is a set of techniques and measures designed to optimize the equipment and facilities of a production plant by eliminating defects, stoppages and accidents. It allows to keep the production equipment in perfect condition, to maximize the effectiveness of the equipment through a maintenance system suitable for its shelf life and improve the reliability of all machines and equipment.
- KANBAN: Information system that harmoniously controls the manufacture of the necessary products in the precise quantity and time in each of the processes. It is also called "card system", acting as a witness of the system to facilitate production.
- VISUAL MANAGEMENT: visual control devices, information, color codes, cards, panels, boards and indicators.
- KPI (Key Performance Indicator): it shows the state of an activity or a process.
- HUMAN FACTOR: Commitment, involvement, training, communication, motivation and leadership, since all personnel are a source that generates value.
- STABLE AND STANDARD PROCEDURES: They are carried out by establishing the structure of the processes, identifying and selecting those that generate value, grouping them by departments and obtaining a process map establishing their interrelationships and evaluating results to incorporate improvements.
- LEVELED PRODUCTION (Heijunka): technique that adapts production to fluctuating demand, connecting the entire value chain from suppliers to interested parties.
- KAIZEN: incorporating changes to improve *(*Kaizen Teian: *individual motivation to incorporate small improvements.* Gemba Kaizen: *collective motivation to encourage opportunities for improvement).*
- TAKT TIME*: time the process should take to deliver a complete, finished product to meet customer demand.* Lead time: *time that elapses from the start of a production process, when an order is generated, until it is completed (including the time of delivery to the customer).* Cycle Time*: The time from when we start working on one product to when we are ready to start the next one within a process or workstation.*
- CONTINUOUS FLOW: coupled operations and processes, which produce an increase in productivity and a reduction of stock and delivery times.
- PULL SYSTEM: system in which the interested parties or clients of the process pull the resources so that their product is generated immediately and without waste.
- AUTOMATIC STOPS: used for the prevention of defective units.
- MAN-MACHINE DIVISION: evaluation of dedication time to carry out the different tasks.
- POKA YOKE *(Inadvertent error prevention):* Helps prevent errors before they happen or makes them very obvious so that the worker realizes and corrects them in time, through the use of devices designed to prevent, control or detect the production of defects in the performance of a service or manufacture of a product.

- JUST IN TIME: Adaptation to demand with the right amount and when requested.
- JIDOKA *(Automation with human intelligence or "Autonomation")*: quality control at the source, preventing a defect from passing to the next process, in contrast to traditional processes where inspections were carried out at the end of the production line, discarding defective products.

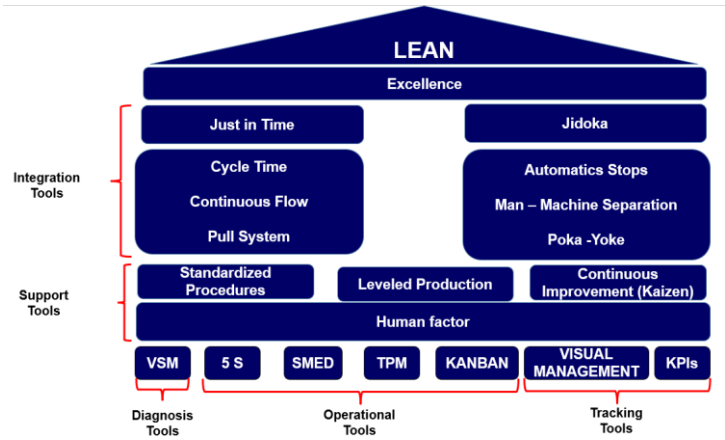

Figure 1. Lean Model: tools (Own preparation)

2.2. Method

A process reengineering must be carried out to incorporate the different Lean tools mentioned above in the industrial manufacturing of the loperamide HCl-ODT production process and its subsequent integration into the PQS, which must be done through the following stages: weighing, sieving, mixing, compression, and conditioning (Figure 2).

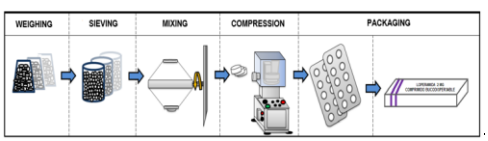

Figure 1. Phases or stages of the industrial manufacturing of HCl-ODT (Own preparation)

The methodology followed is the adaptation of Lean philosophy in a production line of loperamide HCl-ODT based on productive knowledge, and legislation.

3. Results and discussion

In the Lean environment, the aforementioned "value" is defined from the point of view of customer interest, whether internal such as other departments inside the pharmaceutical laboratory, or external as the end customer. In such a way, a specific product or service is offered at the time it is required and in the quantity desired at a competitive cost and price. Therefore, it is essential to simplify the set of processes that add flow of value. Sources of non-quality must be eliminated and the activities that generate them optimized.

The need to eliminate the root causes of non-quality or waste, known in the Lean Management as "Muda" that include excess inventory, lack of storage space, overproduction, unnecessary movements/ transportation and waiting times that do not add value.

Over processing, that is unproductive operations, simplify activities in procedures, avoid unjustified practices, known in the

Lean Management as "Muri"), Defects, Reprocessing and Rejection, are failures and errors that lead to new processing. Early detection of defects, intermediate product identification, verification of critical activities, variability due to lack of standardization, are known in the Lean Management as "Mura".

It is therefore necessary that the management be in contact with the reality of what happens in the so-called "Gemba". The value generated in the production line itself, support real needs. Fluid and standardized communication, supported by indicators or quality indices, is required and called KPIs. Once the Lean diagnostic, operational and monitoring tools is defined, a proposal must be established for the Human Productive Organization (HPO) of the HCl-ODT manufacturing process, as it happens in the definition of the information and communication channels from the origin in the production plant to the management (Imai, 2014).

The management of the human factor (Figure 3) has transcendental repercussions on the results and the success of its management can lie in the policy and practices applied. Job analysis, human resources planning-recruitment-selection-training, performance evaluation, compensation and continuous improvement, are crucial taking into account that these factors may have external influences *(economy, competition, legislation, labor market*) and internal influences (*management support, strategy aligned with the PQS, Lean culture, technologies and organizational structure, etc.)* (Dolan et al, 2014).

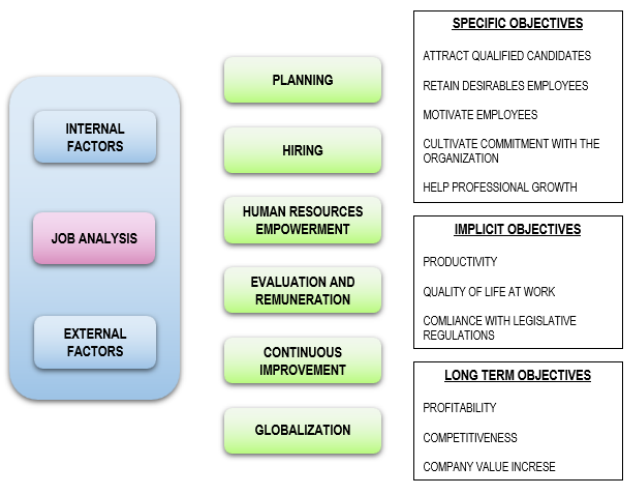

Figure 2. Strategic perspective of human resources management (Own preparation)

The objective of the human factor in the Lean Management is based on teams that facilitate the flow of value, versatile people, trained, involved, motivated, with an open mind to change and with the ability to propose improvements, since they are connoisseurs about the processes (Cuatrecasas, 2016).

The operational actions of a drug production line must be documented in different protocols or standard operating procedures (SOP). It includes all documentation associated with production processes (standard formula, standard method, etc.), staff training, documentary evidence (certificate of analysis of raw materials and packaging material, analytical reports for intermediate and finished products,

requalification, validation, cleaning, etc.), documentation related to support departments (Technical Services Dept., Quality Control Dept., Maintenance Dept., etc.). In order to comply with the NCF and SCF incorporated so that the intermediate product and finished product (HCl-ODT) present a controlled and acceptable variability of the critical process parameters, according to ICH Q9, to guarantee critical quality attributes previously defined or established for the finished product (Agencia Española de Medicamentos y Productos Sanitarios, 2011).

However, although the processes and associated activities in accordance with the before mentioned regulations and the integrating vision of the PQS, Lean proposes a standardized work system. It constitutes the basis, together with the involvement of the worker, to quantify quality, diagnose and improve processes, as well as reduce as much as possible the already known waste. For this, it is necessary to present the tools provided by this methodology, which are compatible with others applied in quality risk management: Failure Mode Effects Analysis–FMEA, Failure Mode, Effects and Criticality Analysis-FMECA, Fault Tree Analysis-FTA, Hazard Analysis and Critical Control Points-HACCP, Hazard Operability Analysis-HAZOP, Preliminary Hazard Analysis-PHA, risk ranking, statistical process control, Control Charts, Acceptance Sampling (by attributes, double, multiple and sequential), Taguchi methods: the Quality Loss Function (QLF), Pareto diagrams, histograms, correlation or dispersion diagram, etc. (Botet, 2012; Gomez, 2018).

The diagnostic tools include the so-called "Value Stream Mapping" (VSM). It is a map of the value flow, which moves horizontally between the different departments involved. It also represents the information flow of both materials and processes. It provides a global and realistic vision of the operations that occur in the Gemba, as well as using a unique and simple language through pictograms and standardized rules, in order to detect "mudas" throughout the flow, that is to say, from the initial stages to the final ones, with the purpose of applying improvements. VSM therefore facilitates strategic planning and change management (Cabrera, 2012; Cuatrecasas, 2016; 50Minutos, 2017).

Figure 4 shows an example or representation of VSM according to the life cycle of the HCl-ODT from the request of the interested parties or clients until its delivery. As can be seen, this map facilitates the vision and understanding of the process and identifies its waste, as well as the sources of competitive advantages.

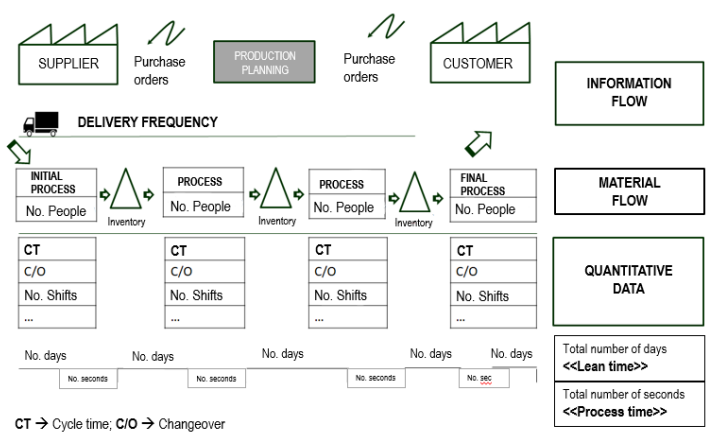

Figure 3. VSM scheme HCl-ODT life cycle (Own preparation)

The 5S standardize the workplace and, in general, constitute the basis for the development of various activities. In addition, it facilitates the standardization of processes by defining the flow of materials, thereby increasing performance and cost savings, as well as the reduction of equipment breakdowns, unnecessary movements, accidents at work, probability of cross-contamination, also facilitating adaptation to the workplace, not only for newly hired personnel but in general for all staff (Hiroyuki, 1997; Cabrera, 2012).

The methodology used in the 5S must be simple, intuitive and visual so that it can be applied throughout the production process as long as it does not pose a risk to the quality of the medicine, such as complementary identification with different colored flanges to distinguish bulks of weighed, sieved and mixed raw material or bulk tablets (Figure 5).

The SMED tool *(S= Single; M= Minute; E= Exchange; D= Die)* reduces changeover times to improve the efficiency of the entire production process (Cuatrecasas, 2016) (Figure 6).

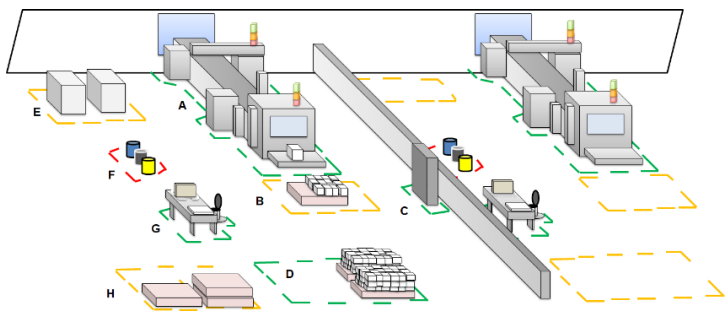

Figure 4. Example: 5S implementation in the HCl-ODT packaging line. Packaging line (A), pallet with packed product (B), wardrobe with less used materials but necessary for the operating process and first level maintenance (C), finished product (D), material (cases, leaflets y boxes) to replenish in the packaging line (E), wastes (F), worktable with documentation related to room and equipment (G), pallet pending use (H), (Own preparation)

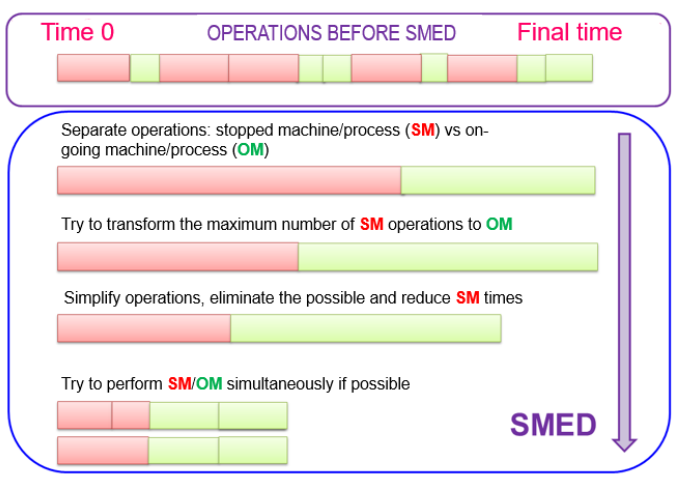

Figure 5. Activities of a process and application of the SMED tool (Own preparation)

As can be seen in Figure 6, before the application of the SMED tool, both the actions with the equipment/process stopped and with the equipment/operational process are intermingled and as a whole present a determined total time. Firstly, a distinction must be made between both families of actions to transform the maximum number of actions with the equipment/process stopped into actions with the equipment/process operational and then, both are simplified to finally combine actions and standardize them in order to reduce the total time of the process. This technique is useful to introduce in production line specifically in the compression machine of the HCl-ODT. It favors flexible manufacturing reducing the amount of time in changeover format for the manufacture of other tablets that share the same equipment. Therefore, this tool is appropriate to reduce the Lead Time, since it achieves a more agile delivery of the resulting product to the next process, reducing costs and obtains greater productivity and performance of the team.

The Kanban tool allows the control of the flow of information and materials, to coordinate the HCl-ODT production process according to the principles of the Pull system, which constitutes the basis of the Just in Time methodology. Since Kanban provides the production control instructions to each work area, it provides a signal that authorizes the production or movement of the products to obtain the required quantity at the requested time. It is very useful the use of the so-called "Kanban boards" and the color-coding, which reflect the situation point (i.e.: green=end of process, yellow=process in progress, red=canceled process) (Cuatrecasas, 2016; Brau, 2016).

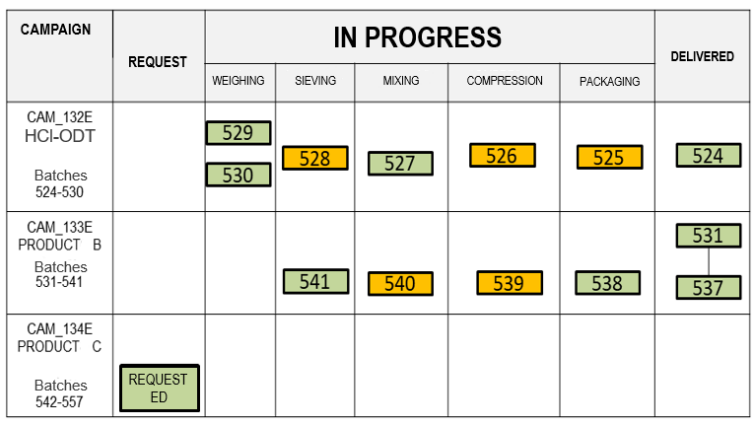

Figure 6. Kanban board example and status-situation of different production batches (Own preparation)

Total Productive Maintenance (TPM), represents a new approach to maintenance management. Its novelty implies the participation of all personnel, overall efficiency, the incorporation of improvements in the equipment's life cycle and the application of an adequate maintenance management system, since all this will affect the Overall Equipment Effectiveness (OEE). It results in the reduction of complaints and manufacturing costs, improvement of the degree of satisfaction of the interested parties and in the reduction of occupational accidents (Cuatrecasas, 2010).

The visual management tools have the objective of facilitating in a practical, simple and easy way the value flow of the

operational process of the materials as well as a standardized communication. This is how immediate information concerning the status of the situation in the Gemba is obtained, detecting sources of expenses. Problems can be quickly detected and most of them solved. Those tools are related to others mentioned above, such as 5S, KPIs, Kanban, and others such as Poka, Yoke, and Jidoka, which will be discussed later.

The Indicators, Quality Indices or KPIs, associated with the different processes must be quantifiable, since quality must be measured, as well as specific, achievable, realistic and with a certain time frame to achieve the proposed objective, in addition to providing necessary and easy to use and interpret information.

For the manufacturing process of HCl-ODT, are proposed the Indicators shown in Figure 8, as follows:

- **OEE** (*Overall Equipment Effectiveness)*: Quantifies productivity and efficiency of production teams. Calculation per turn.
- **FTT** (*First Time Through*): Percentage of suitable units of a process without reprocessing. Calculation per shift, per day or monthly.
- **TEEP** (*Total Equipment Performance*"): Level of use of the means of production. Degree of actual capacity used by the equipment. It takes into account machine and planning losses.
- **TAT** (*Turn around Time*): Measurement of fluidity of Value through punctuality of deliveries. It can be considered as an "internal Lead time". In the HCl-ODT production line, it could be interpreted as the number of "outputs" of a process delivered in a timely manner with respect to the total in a campaign. It could also be interpreted as number of batches delivered punctually with respect to the total in a campaign. monthly calculation.
- **BTS** (*Build To Schedule*): Level of compliance with the production plan. The higher the percentage, the more the production adjusts to the schedule.
- **5S Status**: Level of compliance with the 5S tool. Monthly evaluation.
- **MTBF-MTTR** (*Mean Time Between Failure*, *Mean Time To Repair*, equipment reliability and maintainability): MTBF measures the mean time between two equipment failures. It is associated with its reliability. The total operating time relates to the sum of the times between equipment failures that prevent its proper use during the time that its operation is scheduled. MTTR measures the mean time to repair of a piece of equipment. It is associated with its maintainability. The total stoppage time is that of a equipment as a consequence of the failures it presents.
- **AFI** (Accident Frequency Index): Number of accidents with sick leave during the working day in a period, for every million hours worked. Measures the impact of the production process on worker safety and hygiene.
- **RUPU** (Raw material used per Product Unit): Operational performance indicator that specifies the raw material used per unit of product (Kg/unit).

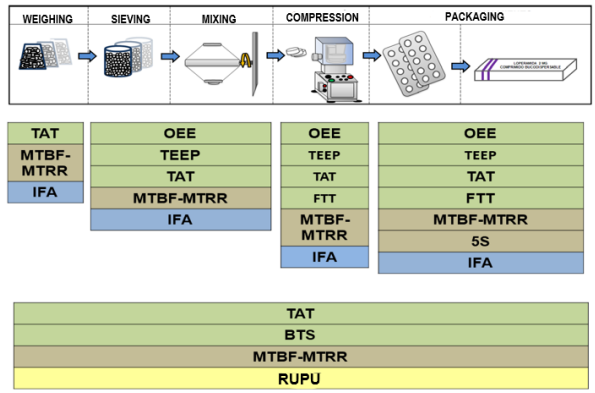

Figure 7. Indicators or KPIs applied in the different phases or steps of the production process of HCl-ODT (Own preparation)

These tools are able to work according to a Pull System: from the request for its manufacture to its delivery, with the involvement of all the processes involved, in order to achieve a continuous flow to meet a "Takt time" or ideal cycle time. It gives a reference of the rhythm necessary to meet the demand and to synchronize the different production processes of the various medicines that are manufactured. In a "Just in time" basis, that is, obtaining the correct product, in the correct quantity, at the correct time, thus avoiding the generation of "non-quality" sources, such as excess overproduction, excess inventories and, ultimately, actions that are not going to generate value (Cabrera, 2012; Hernández & Vizán, 2013).

From this system it is necessary to work according to a level and balanced production (*Heijunka*). It requires an adequate level of flexibility, so it is necessary to have a general and controlled vision of the set of processes (VSM), as well as a qualified human team, who knows how to carry it out through standardized processes, with the help of a series of operational, diagnostic and monitoring tools under a defined work methodology.

The technological advances incorporated in the different equipment and systems in the pharmaceutical field have been able to adapt to the visual management methodology through the incorporation of systems and devices that give them the ability to detect errors that have occurred, both in equipment and in systems. In the language of Lean Management, this methodology is Jidoka, which allows detecting anomalies and stop the process through warnings or alarms. Doing so, the operators proceed to detect the root cause, producing a man-machine separation, since either the equipment corrects the errors, or it facilitates the decision-making by the operator and at the same time avoids the doubt or fear to stop the process.

The ultimate objective of this Jidoka tool is the achievement of zero defects, facilitating the operator's management of different equipment at the same time (Cabrera, 2012; Corral, 2018; Asensi, 2020). Kaizen is the name given in the Lean Management methodology to continuous improvement processes policy. This strategy incorporated into the entire HCl-ODT production chain, since is based on small changes applying common sense, constant effort and cost reduction, the result of in-depth knowledge of the set of processes by the personnel involved.

To obtain the desired results by applying the planning-operation-evaluation-improvement cycle stipulated by the entire Quality

System, it is necessary to channel efforts into the human factor, to cultivate their involvement, training and participation. (Imai, 2014; Gonzalez et al., 2017).

4. Conclusion

A theoretical process planning for the industrial manufacture of loperamide hydrochloride orodispersible tablets (HCl-ODT) has been carried out applying Lean Management.

The Lean Management has demonstrated to be an excellent resource to produce loperamide hydrochloride orodispersible tablets (HCl-ODT) since it improves its Quality System, as well as facilitates compliance with the national and international guides, standards and legislation that apply to it.

This proposal of manufacturing loperamide HCl-orodispersible tablets (HCl-ODT) under the coordination of the Pharmaceutical Quality System (PQS) using the different available Lean tools not only increases efficiency and effectiveness in production but also reduces costs.

The Lean application generates a productive process that is easy to manage, adaptable to changes, robust and standardized from all points of view (operational, strategic and support) so it is advisable to carry out further studies, with different pharmacologically active substances, pharmaceutical forms, and manufacturing laboratories to consolidate the conclusions obtained with this study to medicines, and health products in the pharmaceutical industry.

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