UNIVERSITAT DE BARCELONA
Facultat de Farmàcia
i Ciències de l'Alimentació

Final Degree Project

Pharmacy Degree

QUALITY ASSURANCE AND EXCELLENCE IN A UNIVERSITY PILOT PLANT

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Secondary areas: Legislation and Deontology, and Mathematics and Bioinformatics

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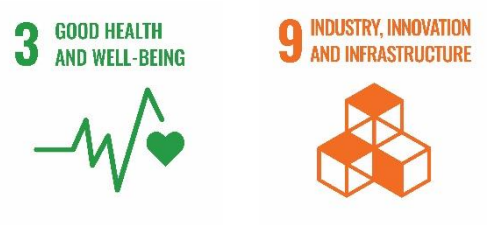

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ABBREVIATIONS

cGMP: current Good Manufacturing Practices

DMAIC: Define, Measure, Analyze, Improve and Control

EMA: European Medicines Agency

FMEA: Failures Mode and Effects Analysis

PD: Pharmaceutical Development (department at SDM)

ICH: International Council for Harmonisation

ISO: International organization for Standardization

PAT: Process Analytical Technology

PQS: Pharmaceutical Quality System

QA: Quality Assurance (department at SDM)

QbD: Quality by Design

QC: Quality Control (department at SDM)

SDM: Service of Development of Medicines (*Servei de Desenvolupament del Medicament*)

SOP: Standard Operating Procedure

TD: Technical Director (at SDM)

TQM: Total Quality Management

ABSTRACT

Quality assurance and excellence in a university pilot plant

Excellence is achieved through continuous improvement, and the most widely used methodology for continuous improvement is *Lean Six Sigma*. This dissertation aims to evaluate whether the tools that compose *Lean Six Sigma* can be applied in a university pilot plant. Taking the SDM as a reference, two processes were chosen, and two *Lean Six Sigma* tools were applied to each of these processes. The time taken to resolve deviations and the quality of documentation were chosen because they had been quality indicators at SDM for several years, which had reflected their importance to the pilot plant. An Ishikawa diagram aided in identifying possible factors contributing to a late resolution of deviations. The subsequent failures modes and effects analysis effectively helped to identify different failures modes and set a risk number to help prioritize the suggested preventive actions to take. Similarly, for the quality of documentation, brainstorming aided in identifying weaknesses and improvement opportunities. The ensuing 5 whys analysis helped pick the possible main obstacles to achieving a high level of client satisfaction with the quality of documentation. Both analysis processes identified personnel as a limitation due to high rotation and the deficient involvement, and training. However, improvement opportunities have been detected as well; the use of FMEA can be helpful in resolving complex deviations, and the improvement of the digital organization system can help attain higher quality documentation.

Key words: excellence, continuous improvement, lean six sigma, pilot plant.

RESUM

Garantia de qualitat i excel·lència en una planta pilot universitària

L'excel·lència s'aconsegueix mitjançant la millora contínua, i la metodologia més utilitzada per a la millora contínua és *Lean Six Sigma*. Aquest treball té com a objectiu avaluar si les eines que conformen *Lean Six Sigma* es poden aplicar en una planta pilot universitària. Prenent com a referència l'SDM, es van escollir dos processos i es van aplicar dues eines de *Lean Six Sigma* a cadascun d'aquests processos. El temps necessari per resoldre les desviacions i la qualitat de la documentació es van escollir perquè són indicadors de qualitat a SDM des de fa diversos anys, fet que reflecteix la seva importància per a la planta pilot. Un diagrama d'Ishikawa va ajudar a identificar possibles factors que contribueixen a una resolució tardana de les desviacions. El FMEA posterior va ajudar eficaçment a identificar possibles fallades i establir un nombre de risc per ajudar a prioritzar les accions preventives suggerides. De manera similar, per a la qualitat de la documentació, la pluja d'idees va ajudar a identificar les debilitats i les oportunitats de millora. L'anàlisi dels 5 perquès posterior va ajudar a escollir els possibles principals obstacles per aconseguir un alt nivell de satisfacció del client respecte a la qualitat de la documentació. Ambdós processos d'anàlisi van identificar el personal com una limitació a causa de l'alta rotació i la deficient implicació i formació. Tanmateix, s'han detectat oportunitats de millora; l'ús de FMEA pot ser útil per resoldre desviacions complexes, i la millora del sistema d'organització digital pot ajudar a aconseguir una documentació de major qualitat.

Paraules clau: excel·lència, millora contínua, *lean six sigma*, planta pilot

INTEGRATION OF AREAS

This project can be related to at least three distinct study areas. Mainly it is related to pharmaceutical technology; additionally it involves other study areas such as legislation and deontology, and mathematics and informatics.

It is firstly related to *pharmaceutical technology* because it is centered on the tools used by the pharmaceutical industry to achieve excellence. Its foremost aim is to evaluate whether it would be possible, and useful, to use such a system in a pilot plant context, at a smaller scale throughout the development process. In second place, it is related to *legislation and deontology* as well since the pharmaceutical industry is a highly regulated industry, and it is progressively held to increasingly high standards. This can be achieved thanks to the quality assurance department who is constantly on top of regulatory demands and continuous improvement. Lastly, it is connected to the subject matter of *mathematics and informatics* being as decision taking is currently based, as much as possible, on statistical data analysis. Additionally, the implementation of changes always has to be preceded by a thorough assessment of the current situation, considering the available knowledge and data, so that safe and informed decisions can be made. Much of the data can be collected through specific software, which can be attributed to informative improvements.

SUSTAINABLE DEVELOPMENT GOALS

This dissertation supports the sustainable development objective number **three** that strives to achieve *good health and well-being*. The quality of medicines, innovation of manufacturing technology and improvement of development steps all translate to a higher quality medical care. As a result, better medical care can occur, which translates to better health and well-being of the masses. This project relates to quality assurance and working towards the implementation of process improvement systems to seek excellence.

Additionally, the context of this project is within a pharmaceutical pilot plant, which participates in the development of medicines and medical devices. Hence, it supports objective number **nine** regarding industry, innovation and infrastructure. With this objective the United Nations Organization wants to *build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation*. Specifically, this project aligns with objective 9.4 designated to upgrade infrastructure and retrofit industries to make them sustainable. We are always looking to achieve greater efficiency when using the resources available by implementing improvements in any system.

Another related specific objective is objective 9.5 which focuses on enhancing scientific research and upgrading the technological capabilities of industrial sectors, in this case, the pharmaceutical industry. This project aligns with this objective because one of the functions that the SDM pilot plant wanted to cover, when it was first established, was offering technological and scientific services for the development of medicines and medical products.

TABLE OF CONTENTS

1. INTRODUCTION

1.1. CONTINUOUS IMPROVEMENT IN THE PHARMACEUTICAL INDUSTRY

Excellence is defined, across all sectors, as the quality of being outstanding, much better than average. Excellence in the pharmaceutical industry encompasses efficiency, productivity, and reliability while undertaking minimal variations and costs. This is achieved through continuous improvement, which implies an ongoing improvement of processes with the goal of improving both productivity and quality while reducing costs, amongst other benefits (*figure 1*). Currently, quality is sought through the concept of Total Quality Management (TQM) which focuses on the prevention of defects rather than their detection (1).

Figure 1. A Closer Look at the Process Excellence Drivers (2).

The general ISO 9001:2015 certification is the most widely used standard regarding quality management, this certification demonstrates that a quality management system has been established, maintained, and promoted by management (3). Additionally, the European Medicines Agency (EMA) recommends that pharmaceutical companies adhere to the ICH Q10 guideline on the Pharmaceutical Quality System (PQS) (3). To assure safety, quality, and efficacy, the regulatory authorities implement strict controls on pharmaceutical products. In fact, regulation impacts every aspect of the pharmaceutical industry (3).

Continuous improvement should not be seen merely as a quality assurance function. The entire organization should have a continuous improvement culture, so everyone is aware of the continuous improvement tools implemented (3). *Lean Six Sigma* is a continuous improvement culture applied all across the world in several industries, including manufacturing, service, healthcare, government, non-profits, and education. But its deepest roots are found in the automotive industry (4). Since the pharmaceutical industry operates in a current good manufacturing practice (cGMP) environment it has

been slower than other sectors to successfully apply *Lean Six Sigma* tools (5). This can be attributed to the fact that cGMP focuses on producing safe and effective products, whereas *Lean Six Sigma* focuses on improvement and added value (5). Some *Lean Six Sigma* tools applied in the pharmaceutical industry are: cause and effect analysis, 5 whys analysis, 5S analysis, process mapping, brainstorming, and FMEA.

There are other excellence techniques that have been used such as Quality by Design (QbD) and Process Analytical Technology (PAT). The former is a methodical approach to drug development that focuses on identifying and controlling the variables that negatively impact product quality. It entails using statistical tools and risk management strategies to ensure that products have their intended characteristics (6). The latter is a system for analyzing pharmaceutical manufacturing process through real-time monitoring of critical process parameters (7). Similarly to QbD its objective is to maintain consistent quality so the product meets its desired characteristics. Similarly to *Lean Six Sigma*, PAT can help improve efficiency, reduce costs and increase product quality. Both of these techniques can be used in pharmaceutical pilot plants, but it can be challenging given the limited resources.

1.2. ICH Q10 ON CONTINUOUS IMPROVEMENT

The ICH Q10 guideline describes a model for an effective pharmaceutical quality system (PQS) based on current ISO quality concepts and GMP regulations. It aims to promote innovation and continuous improvement using science and risk based approaches throughout each of the product lifecycle stages, ranging from pharmaceutical development to product discontinuation (8). It wants to encourage the use of a change management system to guarantee that continual improvement is implemented opportunely and successfully through quality risk management, to evaluate the proposed changes; and through the evaluation of the changes undertaken to support them.

This guideline refers to both recommended activities to further continuous improvement regarding the quality of processes and products, and the pharmaceutical quality system itself (8).

In fact, ICH Q10 aims to encourage continuous improvement while also stating that change should have a high level of certainty and no unintended consequences. As a result, when working on continuous improvement projects, the pharmaceutical industry could become overly cautious of change and focus on the risks of said change instead (3).

1.3. CONTEXT OF THE SERVICE OF DEVELOPMENT OF MEDICINES

The Service of Development of Medicines (SDM, *Servei de Desenvolupament del Medicament*) was created in the Faculty of Pharmacy (currently, the Faculty of Pharmacy and Food Science) at the University of Barcelona. It was established in 1996 in order to upgrade the university's teaching and research opportunities, as well as to further collaboration with the pharmaceutical industry (10).

As a pharmaceutical technology pilot plant, it is divided into different departments including: manufacturing, quality control, quality assurance, analytical development, maintenance, and administration. It currently holds ISO9001 certification of compliance with the current ISO9001:2015 version. Additionally, SDM constantly strives for improvement through the implementation of GMP guidelines.

2. OBJECTIVES

The objective of this work is to analyze the tools used in the pharmaceutical industry that seek to achieve excellence. To later evaluate how these tools can be incorporated into the SDM pilot plant.

3. METHODOLOGY

Firstly, the ICH Q10 guideline about the pharmaceutical quality system was analyzed concerning continuous improvement. This was followed by the analysis of the most common continuous improvement methodologies in the pharmaceutical industry: *Total Quality Management*, *Lean Manufacturing* and *Six Sigma*. This allowed to analyze the most frequently used *Lean Six Sigma* tools to assess their place and value in a continuous improvement system.

Secondly, based on a previous project (10), where the quality indicators used in the pilot plant SDM were analyzed (*annex 1*), the related processes were studied. Two of these processes were selected due to their importance within the pilot plant and the need to improve them. The selected processes were: management and timing to resolve deviations, and documentation management.

Thirdly, two of the previously analyzed continuous improvement tools were applied to each of the selected processes. On one hand, an Ishikawa diagram was conducted focusing on the timing of deviations. Then an FMEA was proposed to be applied to shorten the time taken to resolve deviations or non-conformances. On the other hand, 5 whys and brainstorming were applied to the process of documentation management to

identify those steps were the documentation generated can be refined and how that can be done.

4. RESULTS

4.1. ICH Q10 ON CONTINUOUS IMPROVEMENT

This guideline describes a few activities that should be used to further continuous improvement regarding the **quality of the processes and the products**. These include in the first place, a process performance and product quality monitoring system, not only to help provide assurance of continued capability but to identify areas of continuous improvement as well. Secondly, a corrective and preventive action system resulting from data collected regarding complaints, non-conformances, and audits. Thirdly, a change management system in order to approve and implement changes in a suitable manner. Lastly, a quality risk management system to evaluate proposed changes and to evaluate changes after implementation to confirm the desired results are achieved (8).

Furthermore, the guideline also describes activities that should be used to work towards continuous improvement within the **pharmaceutical quality system**. This comprises a periodic review measuring the achievement of the quality objectives and assessing the process indicators previously established; the monitoring of both internal and external factors that impact the quality system, such as new regulations, guidelines, innovations, or simply changes in the business's objectives; and the evaluation of the outcome of these reviews to better allocate resources and staff training, define a quality policy and its objectives, improve processes and documentation and communicate the results.

The problem encountered with this guideline was that it was made up to be applied to industrial products and processes. Hence, it can be complicated to directly apply it in a pilot plant where there are no repetitive processes since no commercial lots are manufactured.

4.2. PROCESS IMPROVEMENT METHODOLOGIES

The costs of research and development, and industrial production are rising, and business competition is increasing for the pharmaceutical industry as well. Hence, the pharmaceutical industry is increasingly adopting continuous improvement as a means of improving efficiency and reducing costs (3). In order to implement continuous improvement methodologies, a culture revolving around continuous improvement needs to be developed to diminish waste and involve all employees (3). It is for this purpose that most pharmaceutical companies use *Lean Manufacturing*, *Six Sigma*, and *Lean Six Sigma*, or at least one of the former. These constitute traditional basic tools that seek

process improvement in a structured manner, using specific tools to obtain results (11). This suggests usage and engagement in fundamental problem-solving and continuous improvement methodologies. As a matter of fact, *Lean Six Sigma* tools are used and are strongly integrated in the pharmaceutical industry regarding specific processes such as the corrective and preventive action system, deviations, and internal audit system (3).

4.2.1. TOTAL QUALITY MANAGEMENT

Total quality management is a viewpoint established by management that mobilizes all the staff in the continuous search for improvement in order to adjust the quality of processes, products, and services to the customer's needs (12). This quality system wants to ensure quality starting at the concept phase, for all productive and management processes, and in all areas including personnel, machinery, and materials. It demands specific treatment for key steps, analysis of errors and preventive measures, as well as quick response when implementing corrective actions (12).

Nonetheless, as a quality management system, it has some fundamental constraints. Firstly, there is the belief that projects should focus on customer satisfaction rather than bottom line improvements. Secondly, there is no set methodology associated with it as a quality system. Thirdly, it is not taken into account in budgets, resource allocation, project selection, or review systems. Lastly, it does not emphasize the use of quality indicators, making it hard to measure the impact of initiatives (13).

4.2.2. LEAN MANUFACTURING

The concept of *lean thinking* involves determining the value of any process by distinguishing value-added steps from non-value-added steps. As well as eliminating waste so that every step adds value to the process (13). On one hand, its aim is to reduce, or even eliminate waste, and on the other hand, it strives to create value. On this, it differs from GMP's objective, which is to ensure that controls are in place to deliver a continuously safe and effective medicinal product (5).

4.2.3. SIX SIGMA

Six Sigma is an improvement system that can be used by any organization. It aims to identify and reduce, or eliminate, the causes of defects and mistakes in processes. That's achieved by concentrating on the outcomes of processes that are critical to customers. *Six Sigma* methods can help develop strong processes, and eliminate excessive variability in processes, which can lead to poor quality (13).

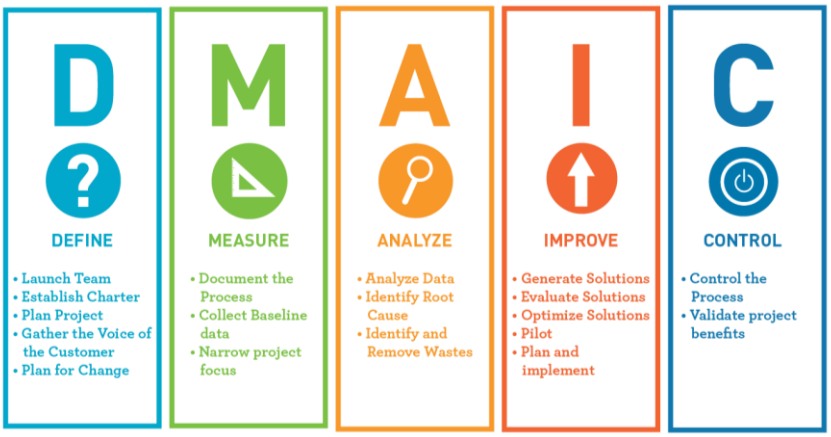


Figure 2. What is DMAIC? (14).

Importantly, and in contrast with *Lean Manufacturing*, *Six Sigma* provides a problem-solving procedure known as MAIC, which originally stood for "measure, analyze, improve, and control", and was later expanded to DMAIC by adding a "define" step at the beginning of the process (*figure 2*) (5). By constructing a process map, the potential constraints arise, and guide the root cause investigation in the proper direction, so the DMAIC structure can be applied (11).

Six Sigma is based on data analysis techniques, these allow to process and interpret data to help make informed decisions. Most data analysis techniques are statistical techniques. A stable process is defined by a Gauss bell. The limits most often set by the pharmaceutical industry are three standard deviations under and over the mean. In this way, it is established that 99,7% of products are found within this range (*figure 3*), hence it is said that the process is stable. Six Sigma takes this process stability a step further, it proposes working with six standard deviations from the mean in order to achieve a very high level of process capability and reduce defects. Using statistical tools, the *Six Sigma*

methodology aims to identify and eliminate causes of variation to achieve process improvement, making defects rare.

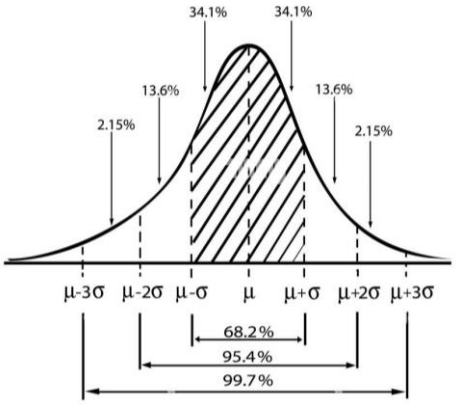


Figure 3. Business and Marketing Concepts, Illustration of 3 Stage Standard Deviation Diagram, Gaussian Bell or Normal Distribution Curve Isolated (15).

4.2.4. LEAN SIX SIGMA TOOLS

Lean Six Sigma combines *Six Sigma* tools with the *Lean Manufacturing* thinking system. It seeks performance improvement and assurance of quality in production and processes while eliminating defects and waste of any kind, including physical resources, time, effort, and talent.

Six Sigma focuses on gathering data in order to apply statistical methods to bewildering problems. *Lean Manufacturing* is applied in a more knowledge-based manner, utilizing time-tested principles. Although both process improvement systems require knowledge and experience, it can be stated that *Six Sigma* is more data oriented whereas *Lean Manufacturing* is focused on the implementation of proven principles based on knowledge and experience (13). For this reason *Lean Manufacturing* is not suited to deal with complex problems requiring extensive data analysis and statistical methods, while *Six Sigma* generally requires several months of data collection to resolve a problem. The fact that *Six Sigma* requires a substantial amount of data is not generally a limiting factor in the pharmaceutical industry where data is collected frequently.

To recapitulate, *Lean Manufacturing* is based on the application of a set of known principles, and *Six Sigma* is based on the application of data analysis techniques (13). A system that combines both *Lean Manufacturing* and *Six Sigma* results in a much more complete process improvement mindset. Such a system is considerably more adequate to the rising standards that the pharmaceutical industry is being held to.

Due to the present competitiveness of the market, pharmaceutical companies are facing a few problems including cost pressures, regulatory requirements, and the need to

improve product quality. On one side, the application of *Lean Six Sigma* approaches allows these companies to improve their efficiency and increase product quality while reducing waste. On the other side, *Lean Six Sigma* can help improve customer satisfaction, regulatory compliance and employee engagement. Therefore, adopting these approaches manufacturers can more easily gain a competitive edge and provide their customers with high quality products (16).

The most used *Lean Manufacturing* and *Six Sigma* tools by the pharmaceutical industry are, in decreasing order of use: cause and effect analysis, 5 whys analysis, 5S analysis, process mapping, brainstorming, and FMEA (3). Less employed tools include Hoshni Kanri, which wants to directly connect the organization's objectives with its' daily activities; statistical-based hypothesis testing, a method used to decide whether a set of data supports a hypothesis or not; and Heijunka, which aims to reduce inequalities in a production process and reduce the chances of overloading it (2).

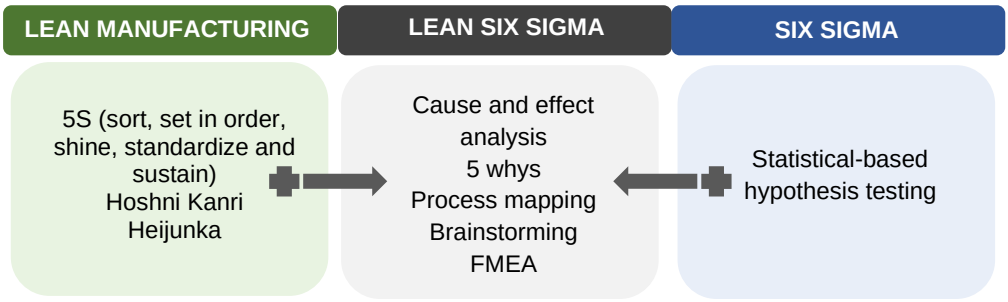


Figure 4. Lean Six Sigma tools. (original creation)

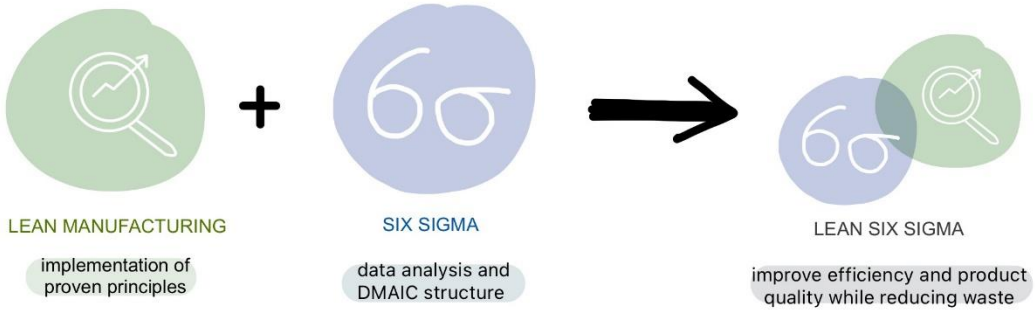


Figure 5. What is Lean Six Sigma? (original creation)

4.2.4.1. Cause and effect analysis

Cause and effect analysis is a technique that helps identify all the likely causes of a problem; this way the main cause can be identified and fixed. This type of analysis is carried out using a fishbone diagram, also called an Ishikawa diagram. These diagrams show in an ordered manner the relationship between a characteristic of a process, or effect, and the factors that contribute to it, or causes. Since most problems result from a series of causes that influence them more or less directly, the first cause of a particular

problem can in time be the effect of a second cause, and so on (17). These diagrams can be helpful in discovering the root cause of a problem and bottlenecks in a process.

Therefore, to face a problem using this technique, the problem is written down in a box on the left and a straight line is drawn to the right. All the factors that can be contributing to this problem are written down and connected to this central line. Once all the possible factors have been identified, the possible causes of the problem related to each one of the factors are identified. Finally, all the identified causes are reviewed to select the most likely ones to plan and put in place corrective actions (17).

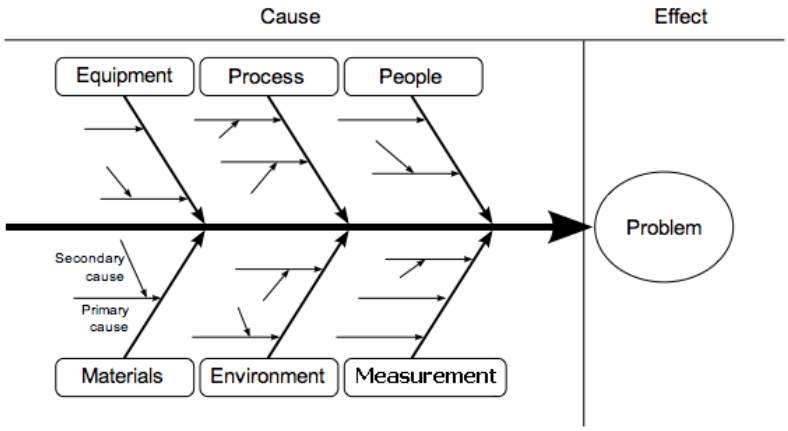


Figure 6. General fishbone Tool of Investigation in Pharmaceuticals (17).

4.2.4.2. 5 whys

The five whys analysis is an iterative and interrogative technique used to find the cause-and-effect relationships underlying a particular situation. The purpose of this technique is to uncover the root cause of a defect by repeating the question “why?” five times. Although in some cases it may require more or fewer whys depending on the depth of the root cause. Each response serves as the foundation for the following question (19). When the counter-measure becomes clear, the appropriate corrective actions are planned and implemented. It is most successful when the answers come from those who have firsthand experience with the process or problem at hand.

The main advantage of this technique is that it is straightforward and powerful without being a statistical analysis tool, which requires a more complicated evaluation. It is helpful not only to identify the root cause of a problem but also to understand the relationship between various root causes. Notwithstanding, it is only an appropriate tool to face simple problems and problems that involve human factors.

However, this technique often oversimplifies the process of problem-solving since it forces users down a single pathway. In addition, it presumes that the last why is the most effective step to enforce a corrective or preventive measure (20).

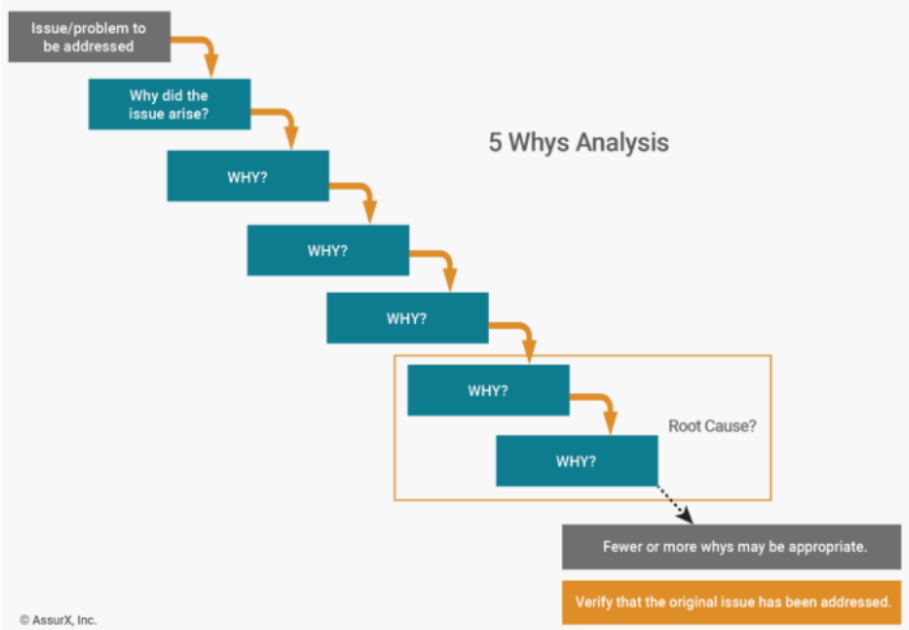


Figure 7. The objective of 5 Why is to keep proving until you are certain the root cause of a problem has been identified (21).

4.2.4.3. 5S

The 5S methodology is a systematic approach for handling workplace organization. It aims to create a workplace that's clean, uncluttered, safe, and well-organized to help reduce waste and optimize productivity, in order to build a quality work environment and maximize efficiency and profit. In fact, this methodology is often considered the foundation of *Lean Manufacturing* because for a workplace to reduce waste and become more efficient, it needs to first be organized.

This methodology originated in Japan as a way to make just in time manufacturing possible. This tool receives this name referring to five Japanese terms used to describe the steps of the 5S system of visual management. Each term starts with an S in Japanese, which translated to English become: Sort, Set in Order, Shine, Standardize, and Sustain (22).

Figure 8. Understanding the 5S's of Kaizen (23).

4.2.4.4. Process mapping

Process mapping is a method which promotes a better understanding of processes and the identification of inefficiencies and areas of improvement (24). This tool is a visual method to represent workflows and processes so they can be communicated in a concise and simple manner. Any process map outlines the individual steps within a process starting at the most general level and providing more detail when necessary. In fact, there is a variety of process maps with different focus points.

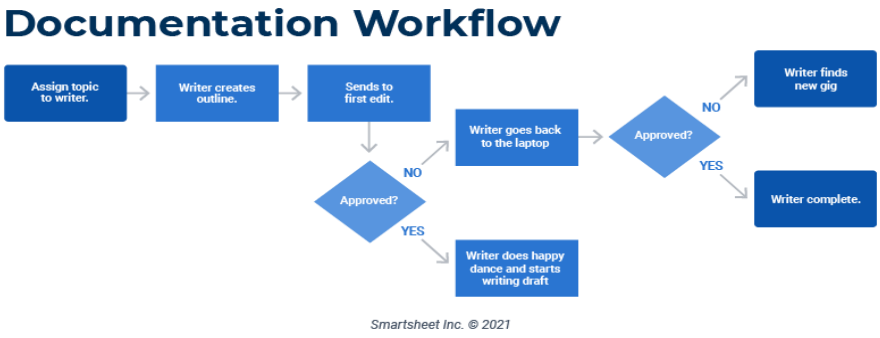


Figure 9. Documentation workflow (25).

4.2.4.5. Brainstorming

The brainstorming technique is used to analyze and solve problems. It is based on the encouragement of a creative and communicative atmosphere in order to produce thoughts and ideas for consideration. It is critical to do it in a group and to do it freely in order to come up with the greatest number of ideas that could provide solutions to specific problems (17), so criticism should be avoided during these sessions. All the ideas should be reviewed at the end of the session in order to explore solutions in depth.

Figure 10. Mindmapping (26).

4.2.4.6. FMEA

Failure modes and effects analysis, or FMEA, is a step-by-step approach for identifying all the possible failures in a design, a manufacturing or assembly process, or a product or service. Failure modes refers to every way in which something might fail, and effect analysis refers to the evaluation of the possible consequences to those failures. Essentially, it is a preventive technique that seeks to identify, evaluate and minimize potential risks that could harm the quality of a product or process, before they occur. It serves to anticipate the appearance of problems: identifying the risks of potential defects, prioritizing through risk assessment, and planning the introduction of corrective measures to reduce the risk until it is eliminated, so more reliable processes can be created. It is essential for continuous improvement (17).

An FMEA should be executed by a multidisciplinary team with individuals from different departments. The system is broken down into simpler, more specific parts to delimit each area and to be able to identify possible failures more easily; these parts can be products, designs or processes. The possible failure modes, its effects, causes and detection methods are established for each one of the parts. Every failure mode is evaluated according to the severity, probability of occurrence and probability of detection in order

to calculate a risk priority index. This index is used to prioritize the more crucial failure modes according with the criticality of the process, and plan and apply corrective actions to reduce or eliminate them.

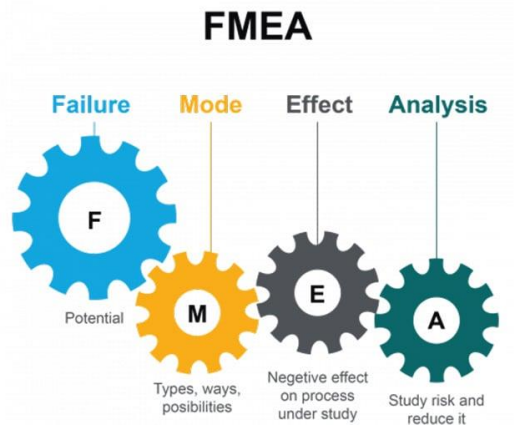


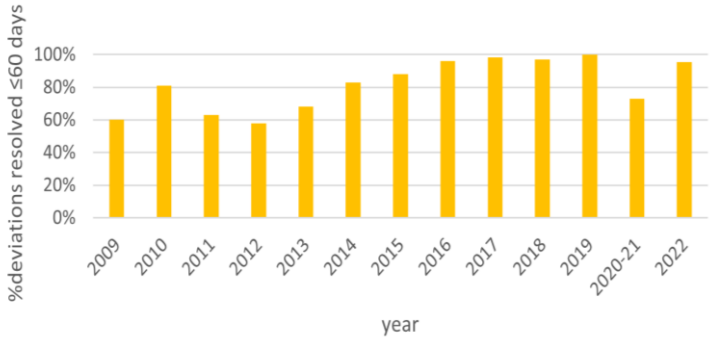
Figure 11. Risk Analysis – FMEA (Failure Mode Effect Analysis) (27).

Recently, in January 2023, a new version of the guideline ICH Q9 about Risk Quality Management was published. This guideline states that quality risk management encourages a scientific and practical approach to decision-making (28). This process is based on the current available knowledge and the assessment of the probability, severity, and detectability of the hazards. In this context, it mentions FMEA, among others, as a risk management tool used in the pharmaceutical industry.

4.3. ANALYSIS OF THE PROCESSES IN THE PILOT PLANT SDM

4.3.1. MANAGEMENT OF QUALITY DEVIATIONS IN SDM

A deviation is defined as an unexpected or unplanned event or situation that can cause harm or disruption to people or the processes, a deviation always requires a response or action (29). The timing taken to resolve deviations is both an ICH Q10 requirement and an ISO9001:2015 requirement. For this reason, it has been used as a quality indicator in the SDM pilot plant since 2009. The graph below shows the percentage of deviations resolved with a difference of 60 days or less compared to the planned date (*graph 1)*, the goal being for 80% of deviations to be closed within that time frame.



Graph 1. Percentage of deviations resolved with a difference of 60 days or less between the planned resolution date and the real resolution date between 2009 and 2022 (10).

It is vital to be able to detect deviations since an undetected deviation will go unresolved indefinitely, which can create further problems. So, regardless of the time it takes to resolve them, or the amount of deviations that are detected, it is considered favorable that they have been detected in the first place. To assess the current situation, the timing of deviations filed between 2018 and 2022 was analyzed. In the pilot plant SDM, 134 deviations were filed in this period of time, and 107 of those deviations were resolved on time. That represents 79,85% of the deviations filed, see *table 1*.

Table 1. Resolution of deviations: planned dates of resolution and timing of resolution. (original creation)

DEVIATIONS FILED BETWEEN 2018 AND 2022	ABSOLUTE NUMBER (deviations)	PERCENTATGE (%)
Number of deviations filed	134	100
Number of deviations resolved within the specified time	107	79,85
Number of deviations that had a planned resolution date	59	44,03
Number of deviations that where resolved within 30 days of being filed (with and without a planned resolution date)	62	46,27
Number of deviations that had a planned resolution date and where closed within 60 days of that date (quality indicator)	48	81,36

On average, taking into consideration the last five years, 126 days is the period of time given to resolve each deviation, see *table 2*. Taking a closer look at the deviations that were not managed on time, which is the indicator to be improved from the quality assurance point of view, they take on average 77 additional days to resolve. That means, regardless of the total amount of time dedicated to resolving this deviation, there is a difference of 77 days between the planned date to have each deviation completely

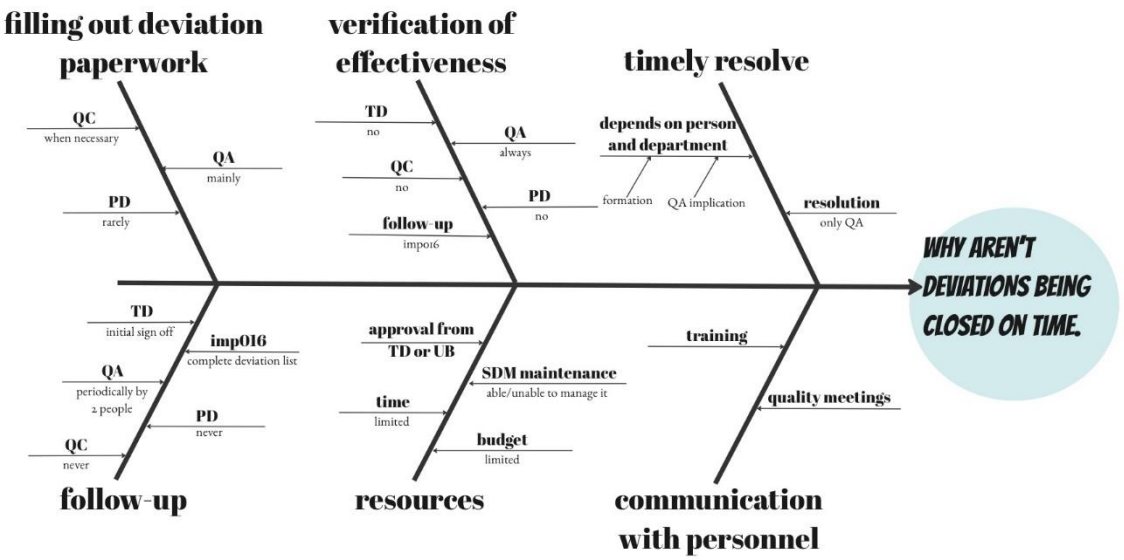
resolved and the real date on which this deviation was resolved. By utilizing *Lean Six Sigma* tools, we want to understand why the set time frames are not being met, and how they can be improved.

Table 2. Days taken to resolve deviations each year between 2018 and 2022. (original creation)

DEVIATIONS	**2018**	**2019**	**2020**	**2021**	**2022**
Number of deviations filed	43	39	9	12	29
Deviations closed in ≤5 days	15	12	1	1	9
Deviations closed in 6 to 10 days	4	4	1	2	0
Deviations closed in 11 to 20 days	3	0	1	0	4
Deviations closed in 21 to 30 days	2	3	0	0	2
Deviations closed in 31 to 60 days	3	3	0	3	4
Deviations closed in 61 to 90 days	5	3	2	0	5
Deviations closed in 91 to 180 days	2	5	2	5	4
Deviations closed in >180 days	9	9	2	1	1
Average planned resolution time (in days)	206	156	99	124	45
Average real resolution time (in days)	91	96	109	98	47
Additional time taken to resolve deviations (in days)	102	62	107	56	57

4.3.1.1. Ishikawa diagram

An Ishikawa diagram, or fishbone diagram, is a very visual tool that is helpful when working in a team. This way the possible causes are grouped into different categories impacting the problem at hand (30). It is a more structured approach than some other tools available for brainstorming causes of a problem (31). It is important to take into consideration all possible causes of mistakes and not only those that have been previously identified (32). In this case, the problem is that deviations have been taking longer than expected to be resolved. To be able to identify the root cause of these unexpected delays when settling the detected deviations, an Ishikawa diagram was drawn, as seen on *figure 12*.



QC: Quality Control
PD: Pharmaceutical development
QA: Quality Assurance

TD: Technical Director
SDM: Service of Development of Medicines
UB: University of Barcelona

Figure 12. Ishikawa diagram of deviation resolution timing at SDM. (original creation)

4.3.1.2. FMEA

Failure Modes and Effects Analysis is primarily a preventive tool. However, FMEA can be used retrospectively to correct a specific problem rather than proactively to prevent potential issues, as it is intended to (33). In such a scenario, FMEA is used as a corrective tool, helping to identify the cause or causes of the failure so they can both be corrected and prevented from occurring in the future. In this rather reactive case, it can be considered a continuous improvement tool as well.

An example of a deviation where using an FMEA could have been beneficial is deviation number 910, filed the 22nd of November 2021. On this day, it was detected that the date when a reactant was being first used was not being registered. It was seen that this had been occurring because the SOP that was supposed to state the necessity of recording the opening dates of each reactant had been lost. The corrective action proposed at the time was to register when each reactive agent was used for the first time, even the ones that had been previously used but not registered, and to start registering the opening date for the new reactants. In later self-audits, this was verified and it had been implemented correctly, so the deviation was considered resolved.

In that case, the following FMEA could have resulted as follows:

Table 3. Example of what an FMEA used to resolve a deviation using deviation number 910. (original creation)

PROCESS	FAILURE MODE	FAILURE EFFECT	SEVERITY (1-3)	POTENTIAL CAUSES	OCCURRENCE (1-3)	CURRENT CONTROLS	DETECTION (1-3)	RISK NUMBER (1-27)	ACTION
Registration of opening date of reactant containers	Not registering the opening date of a new batch of a reactant	<u>Safety risk</u> It can be difficult to determine how long the agent has been in use, and whether it has been degrades or become unstable.	2	Lack of record keeping SOP Human error Lack of awareness or training	2	None	2	8	Date all the opened reactants with the current date. Implement a clear and standardized record-keeping procedure. Train team on accurate record-keeping and the potential consequences. Regularly check and audit record-keeping systems.
		<u>Quality risk</u> It can be difficult to establish whether the reactants is still within its specified shelf life. This can affect the quality of the final product.	3	Lack of record keeping SOP Human error Lack of awareness or training	3	None	2	18	
		<u>Regulatory non-compliance</u> To not know what would happen if they were audited and this was detected for the very first time.	2	Lack of record keeping SOP Human error Lack of awareness or training	2	None	2	8	

By being required to go through the process of identifying possible failure effects and causes, there is already an increased involvement of everyone involved.

4.3.2. MANAGEMENT OF DOCUMENTATION

Documentation is a process that consists of recording, organizing, and storing information about a particular subject or project. It provides evidence or records, in this case, the work that's being done in the SDM pilot plant. It can later be referenced or analyzed to help improve the processes and activities being conducted. Furthermore, it is essential to ensure compliance with current regulations, as it is a requirement from ISO9001:2015, cGMP and both ICH Q9 (Quality Risk Management) and ICH Q10 (Pharmaceutical Quality System).

The implementation of an effective quality management system is supported by the proper documentation. Said documentation includes information describing processes,

procedures, and controls. It should be reviewed and updated according to established criteria, and any quality management activity or change implemented must be communicated to everyone involved (33).

On the one hand, storing the necessary documentation is essential for ensuring the quality of the products and the work done. Accurate documentation of any work, such as the materials and equipment used and the testing procedures, helps identify any possible issues. In time, that allows for corrective actions if needed. On the other hand, if it is required, it allows for a detailed analysis of the process in order to identify areas where improvements could be made to optimize it. Hence, it helps work towards continuous improvement. Documentation is also key to transferring knowledge from the pilot plant back to the customer. By keeping detailed documentation, the knowledge gained during the development process in the pilot plant is not lost.

When a service or project is accepted at SDM, all necessary protocols are created by each department: pharmaceutical development (PD) and quality control (QC). PD creates a protocol, and CQ creates validation and stability protocols. Every activity that is conducted follows these protocols, and all the primary data obtained is registered in a designated notebook to ensure data integrity. The work performed and the results obtained are exposed in a final report, or progress reports if the project is long. So once a service or project is finished, a single report is written by PD, and several reports are written by QC in accordance with the tasks completed (certificate of analysis, and validations, stability, development, and analytical development reports). This process is seen in *figure 13*.

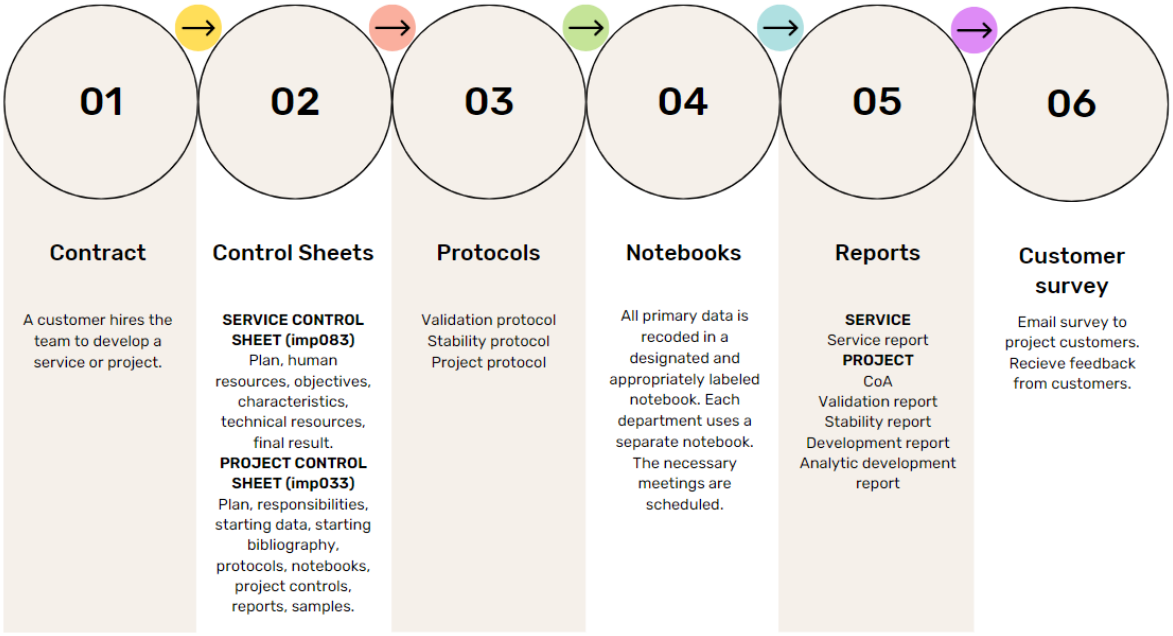
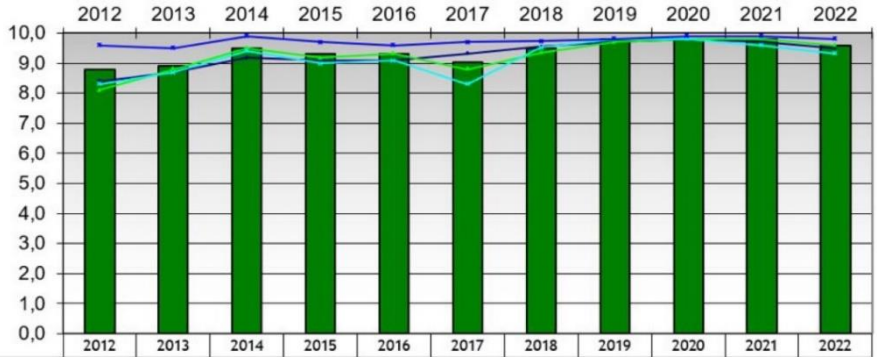


Figure 13. Steps to follow from the start to the end of a service or project at SDM. (original creation)

The optimization of documentation has been used as a quality indicator since 2016. because filling out and keeping the right documentation is vital to an efficient quality system. Specifically, the amount of actions taken towards improving the management of documentation within the pharmaceutical development department has been measured. The aim is to implement four optimization activities per year. This has been achieved to varying degrees, with 1 action taken in 2020-21 and a maximum of 11 actions taken in 2017 (*annex 1*).

Additionally, because of its importance as part of the pharmaceutical quality system, the degree of satisfaction with the quality of the documentation provided is one of the four questions asked on the survey sent to customers when their project is finalized. At the pilot plant, the objective is to achieve a score of 7 or higher, out of 10, on all surveys for each of the four questions. These four questions have been used since 2010, and the average score is often high. This indicates that clients tend to be satisfied with the work provided, and that's an important quality indicator. Nevertheless, the quality of documentation consistently receives a lower score (*graph 2*).



	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Overall result	8,8	8,9	9,5	9,3	9,3	9,0	9,5	9,8	9,8	9,8	9,6
1.Overall score	8,4	8,7	9,2	9,1	9,1	9,3	9,5	9,7	9,8	9,7	9,5
2.Technical quality of the product/service	8,1	8,8	9,5	9,2	9,3	8,8	9,3	9,7	9,8	9,8	9,6
3.Quality of documentation	8,3	8,7	9,4	9,0	9,1	8,3	9,5	9,8	9,8	9,6	9,3
4.Relationship with staff	9,6	9,5	9,9	9,7	9,6	9,7	9,7	9,8	9,9	9,9	9,8

Graph 2. Client satisfaction and feedback from concerned parties: client satisfaction survey (35).

It is for the two reasons mentioned above that the use of the *Lean Six Sigma* tools in this process can be beneficial. The two tools proposed are brainstorming and 5 whys.

4.3.2.1. Brainstorming

Firstly, brainstorming is used since it is a simple process for generating a large number of ideas. This helps to bring forward both obvious and less straightforward ideas to take into consideration later. In this particular case, the aim was to come up with alternative ways in which the documentation could be managed. As well as possible changes that could be made to the structure or content of the documentation itself. With all the options available, a decision-making process begins with the evaluation of all the ideas and

considering multiple perspectives. The ideas reached in this session with the representatives of the QC, PD and QA departments are shown in *figure 14*.

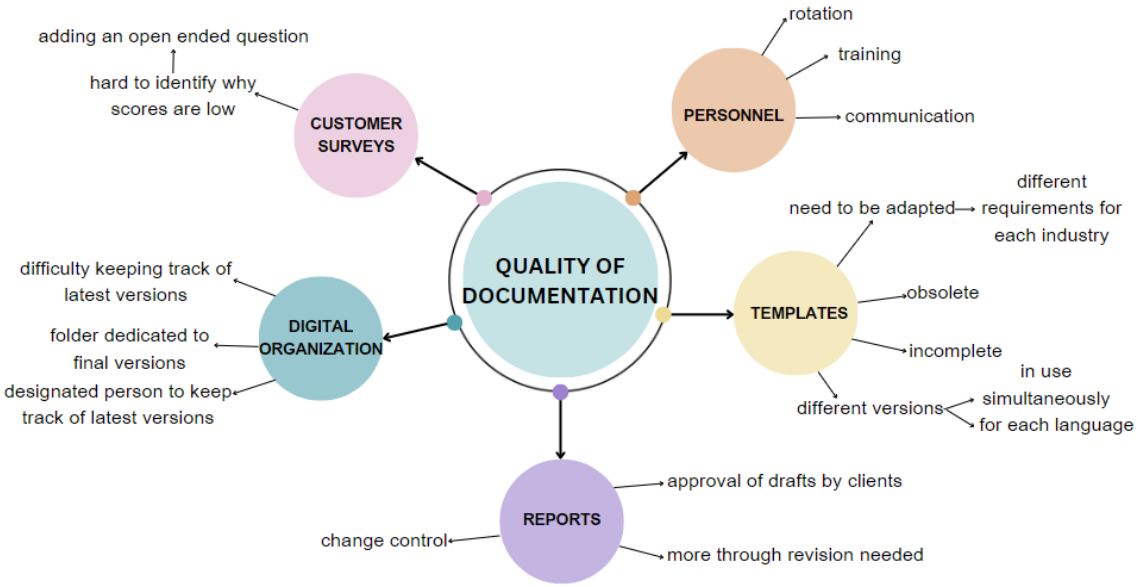


Figure 14. Brainstorming about barriers to achieving higher quality documentation and customer satisfaction based on staff ideas. (original creation)

4.3.2.2. 5 whys

Once everyone had the chance to reflect on the new possible options, 5 whys was applied with the heads of the departments involved (*figure 15* and *figure 16*). 5 whys requires deeper knowledge of the process at hand. Therefore, focusing on the more experienced individuals involved in the process helps narrow down the possibilities. For this reason, this tool was applied by the QC and PD department heads. It is more of a

problem-solving tool than brainstorming, so it is beneficial to apply it after exploring a variety of options during brainstorming.

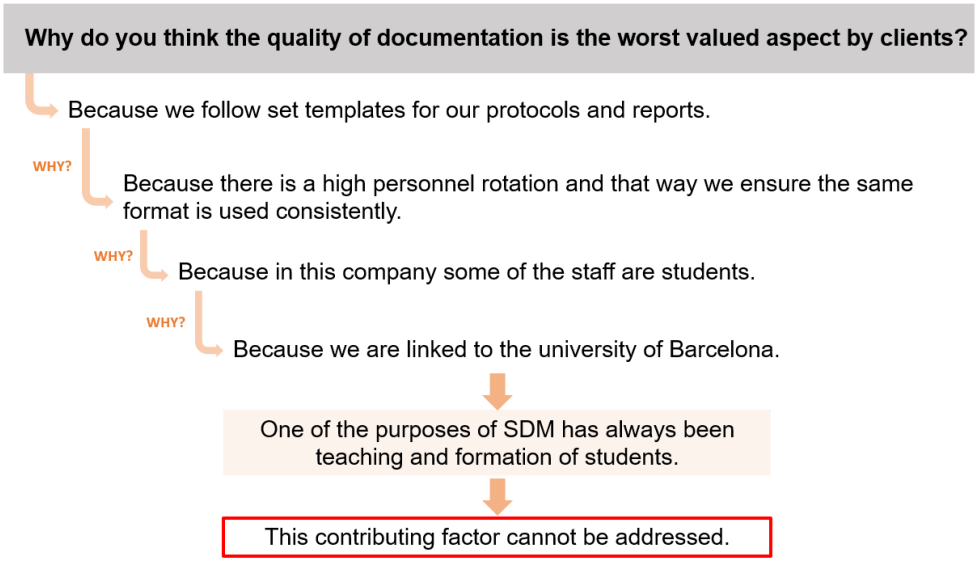


Figure 15. 5 whys solved by the PD department head. (original creation)

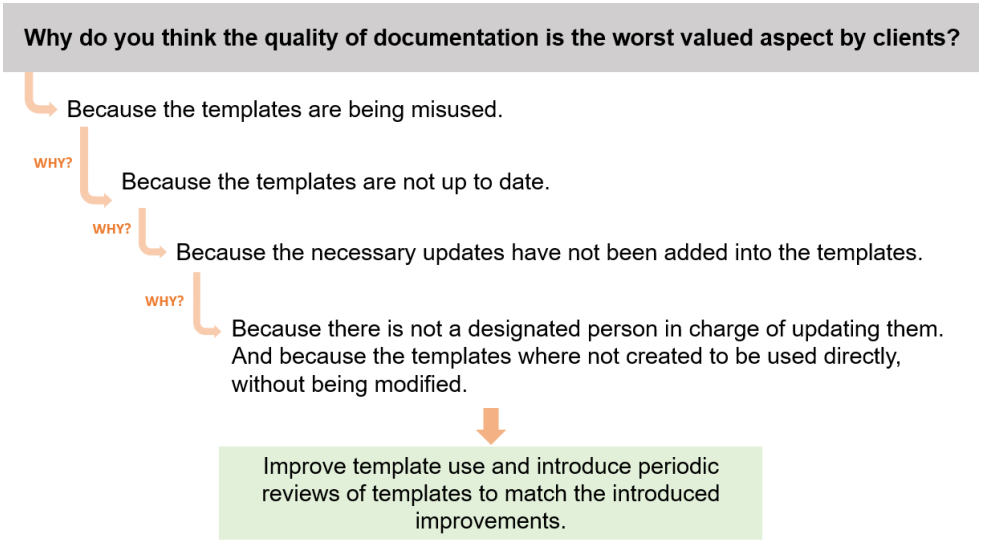


Figure 16. 5 whys solved by the QC department head. (original creation)

5. DISCUSSION

5.1. TIMING OF DEVIATIONS

As seen on *table 1* between 2018 and 2022, 134 deviations were filed and 107 of those were closed on time. That represents 79,85% of the deviations filed. The criterion followed at SDM is that a deviation is resolved on time if it is resolved by the set planned resolution date. If a deviation is filed and no planned resolution date is set it is always considered to be closed on time as well. This gives the unfunded perception that deviations are being managed in a timely manner since only 59 of the 134 (44,03%) filed deviations were given a planned closing date. Notwithstanding, 81,36% of the deviations

with a recorded planned resolution date were resolved within 60 days of said date, which meets the goal stated in the table of indicators.

Table 2 clearly shows an improvement from 2018 to 2022 in the timing of resolution of deviations. The year with the shortest planned time frame to resolve deviations was 2022 with 45 days (days passed between the filing date and the planned resolution date), and the longest time frames were given in 2018 with 206 days. Regarding the real time taken to resolve them, the average is 88 days. 2022 was the year where deviations were settled the fastest, in an average of 47 days (days passed between the filing date and the real resolution date). While 2020 was the year with deviations going unresolved the longest, with an average of 109 days between the day where the deviations were first filed and the day they were resolved. This could be attributed to the COVID-19 pandemic since work was interrupted for a period of time.

By utilizing *Lean Six Sigma* tools, we wanted to understand why the set time frames are not being met, and how they can be improved. Because, regardless of the total amount of time dedicated to resolving each deviation, there is a difference of 77 days between the planned date to have each deviation completely resolved and the real date on which this deviation was resolved.

As seen on the previous Ishikawa diagram (*figure 11*), some reasons why a deviation can take longer to be resolved in the specific context of the SDM pilot plant may be: a complex root-cause analysis, the availability of resources, and challenging communication and coordination with the team. Through experience, the main limitation in the SDM case is the restricted **resources** available for the most complex deviations and non-conformances. Nevertheless, a higher level of **commitment**, from every department involved, could be beneficial to improving the resolution time of most deviations. As seen on the diagram, the filing out of paperwork, follow-up and verification of effectiveness, and resolution, are all mainly performed by the quality assurance (QA) department. That could be attributed to the fact that other departments are more focused on fixing a given issue, deviation, or non-conformance to keep up with the workload. While the QA department is actively exploring new chances to improve the functionality of the activities carried out to the extent of their abilities. In fact, the ICH Q10 guideline recognizes the importance of the QA department to manage deviations within a robust quality management system (8). This is a less common initiative from other departments.

Better communication and higher commitment, as well as helping to identify the cause of a deviation, could be achieved by resorting to a failure modes and effects analysis. Additionally, involving the whole team in the FMEA helps gain a more comprehensive

understanding of the deviation (36). This could be done whenever a complex deviation is identified, since it is natural that these deviations take longer to resolve. Thus, aiding the search for a corrective action for said deviation. With this, the time required to resolve a deviation could be shortened and better adjusted to the time planned to have it resolved. In addition, this would provide possible preventive actions to implement and work towards continuous improvement and higher quality processes and products, to work progressively towards excellence.

Given that team awareness is generally low, it could prove challenging to request participation to fulfill an FMEA. Consequently, it would be important to choose deviations or non-conformances that concern the team, so the added value of this analysis is clearly brought forward. An FMEA could be done for the unresolved deviations during the quarterly quality meetings with the entire team. With this, steps such as following-up on the state of the deviation and verifying the effectiveness of the corrective measures taken could fall on different individuals. Similarly to the experience carried out by Alsaidalani R and Elmadhoun B in 2022, by involving a broader part of the team, more experiences are being considered (36). This way, the chances of effectively addressing the issue are higher and, in time, that promotes a problem-solving mindset.

Long-term, a more in-depth analysis of a deviation could prove useful to detect future deviations earlier. Making it simpler to apply corrective actions. It would help prevent them entirely. However, that's a high standard to hold any company to.

5.2. MANAGEMENT OF DOCUMENTATION

It is important to note that both department heads consulted were mostly satisfied with the templates used to create protocols and reports. Consequently, the issue had to do with the use of these templates. The survey sent to project customers only asks for a score regarding the level of satisfaction with the quality of the documentation provided. This makes it virtually impossible to identify which aspect of the documentation they are dissatisfied with, unless a deviation or non-conformance has been clearly identified. Adding an open-ended question to the survey could be useful to obtain information that could be directly applied to improve the quality of the documentation. For example a question such as: *how could we improve the documentation provided to better meet your standards?* Although these kinds of questions are more reliable, as Duane F. Alwin found in 2007, they are often left unanswered since they require more time and thought than simply giving a score (37). Hence, it is important not to add too many open-ended questions because that could discourage customers from answering the survey at all.

The limitations identified during brainstorming are the templates, the digital management, and the staff. The **templates** were originally devised to be modified according to the project at hand and the demands of each particular customer. Notwithstanding, they are usually not adapted unless the client requests it when they receive them for approval. The fact that the templates are not being modified when a protocol or report is written can be partially attributed to a lack of staff training. The **staff** at SDM is partly composed of students and inexperienced graduates; this means that there are people being formed constantly and that staff rotation is high. To address this, training all the staff periodically could be beneficial since a lack of experience and confidence can be a barrier to change an established template. McDermott O. found that staff training is a critical success factor for the implementation of *Lean Six Sigma* (3). Therefore, in the SDM context these training sessions would be focused on how the templates need to be modified according to the needs of each service and project, how they've been modified in the past, and the correct way to modify them.

It also has to be taken into account that SDM works for different industries, such as the nutraceutical industry, the pharmaceutical industry, and the veterinary industry. Each of these industries has different needs and requirements. To facilitate the modification process, different templates could be created for the same kind of document. By having a template adapted to each of these industries, their demands could be met from the start, leading to higher customer satisfaction. In time, this could be taken a step further by creating a template that incorporates the known requirements of recurrent customers.

Lastly, the **management of the digital files** is also identified as an obstacle. Often, previous reports and protocols are used instead of the defined templates. This easily creates new issues since the information can be interpreted differently and the structure of an old document may have undergone modifications, so there will be missing information or incorrect data on the new document. Moreover, templates have different official versions. When using an old document instead of a template, the latest version can be overlooked. Creating a digital index (38) that directs the user to the right template would simplify the location of each template so no mistakes, intentional or otherwise, are made. With this step towards digitalization, and as stated by Hole G. in 2021, the aim is to help improve efficiency and flexibility.

Even when a final report is sent, the client may ask for changes or for new information or data to be added. So, frequently, there are several "final" versions of a report; this complicates keeping track of these reports and identifying the latest versions and even the final version of a project report.

It is broadly agreed that the **high staff rotation** is a problem for ensuring and maintaining quality in general. The quality of documentation is no exception. This situation can make it so different people are in charge of writing a specific protocol or report at different times. Unfortunately, this causes mistakes to accumulate. Nevertheless, training students and inexperienced graduates to prepare them to work in the pharmaceutical industry was one of the reasons why the SDM was originally created (9). So, a high staff rotation is an inherent characteristic of the structure at the SDM. This cannot be fully remedied and it will continue to be a limitation to maintaining quality.

Overall, both *Lean Six Sigma* tools chosen helped identify multiple limiting factors and improvement opportunities. It is important to remark that when using 5 whys both department heads quickly identified the high staff rotation as the problem, and as mentioned, this cannot be solved. So one of them was asked to take it in an alternative direction. This exemplifies that 5 whys assumes that the first option the person thinks of is the root cause of the problem, whereas in reality a problem has multiple causes and therefore multiple possible improvement opportunities. This issue was also identified by Card AJ in the paper published in 2017; the first pathway identified is neither the only one nor the most important, and there is no objective way to pick a single pathway (20).

6. CONCLUSIONS

Considering the results previously detailed and the objectives set at the beginning, the conclusions reached are the following:

1. Excellence is achieved through the implementation of continuous improvement methodologies.
2. The most widely used process improvement methodology in the pharmaceutical industry is *Lean Six Sigma* which incorporates both *Lean Manufacturing* and *Six Sigma* principles.
3. *Lean Manufacturing* is based on the application of a known set of principles whereas *Six Sigma* is based on the collection and interpretation of data. For this reason they have different scopes of implementation.
4. The tools most used by the pharmaceutical industry belonging to the Lean Six Sigma methodology are: cause and effect analysis, 5 whys analysis, 5S analysis, process mapping, brainstorming, and FMEA.
5. The *Lean Six Sigma* tools can be applied to some extent to any process, even at a smaller scale in a university pilot plant.
6. Each tool has advantages and is most practical in a concrete situation.

a. An Ishikawa diagram is helpful to put together all the contributing factors of a particular process and can be a single knowledgeable individual.
b. An FMEA and 5 whys require a deep understanding of the process and working methodology, so they should be applied by experienced individuals.
c. Brainstorming is a simple tool so it can be used with the entire team to help produce more original and less obvious aspects that contribute to the process in study.

7. Small improvements can be progressively introduced at SDM for continuous improvement. The *Lean Six Sigma* tools selected helped identify these opportunities and risks. The improvement proposed are:
    a. Timing of deviation resolution:
        i. Implement use of FMEA during the quarterly quality meetings to discuss unresolved deviations.
        ii. Training sessions focusing on the procedures followed at SDM and raising staff awareness.
    b. Management of documentation:
        i. Add an open-ended question to the customer satisfaction survey to learn what customers are dissatisfied about.
        ii. Set an adapted template for the protocols and reports for each industry or recurring customer.
        iii. Improve digital management of documentation.

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ANNEXES

ANNEX 1: Monitoring of the quality indicators used in the pilot plant SDN between 2007 and 2022. (X = indicator not implemented that year)

INDICATOR (2022 objective)	2022	2020-21	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007
Quality meetings (≥4) *(figure 1)*	5/4	2/4	8/4	11/4	16/4	NA	3/6	4/6	5/6	5/6	6/6	6/6	7/6	7/8	4/8
Deviations detected outside QA (≥25%)	25%	40%	46,34%	65,91%	46%	14 (1/month)	X	X	X	X	X	X	X	X	X
Deviations detected by PD (≥5%)	4%	0%	9,76%	13,64%	X	X	X	X	X	X	X	X	X	X	X
Marketing actions (≥5) (*figure 2)*	19	0	5	7	X	7	5	15	15	33	29	19	29	13 (≥1)	1 (≥1)
Publications in impactful journals (≥1) *(figure 3)*	4	16	5	9	4	6	5	4	4	1	2	1	5	X	X
Publications in general journals (≥1)	1	11	1	2	1	4	X	X	X	X	X	X	X	X	X
Posters (≥4)	6	9	11	13	23	15	X	X	X	X	X	X	X	X	X
Participation as speakers (≥1)	2	4	2	1	5	X	X	X	X	X	X	X	X	X	X
Collaborators (≥5)	22	11	X	X	X	X	X	X	X	X	X	X	X	12	9
Budget acceptance (≥10%)	100%	28%	28,29%	48,65%	9,52% (≥50%)	X	X	X	X	X	X	X	X	40% (≥10%)	58,3% (≥10%)
Agreement renovation (100%)	100%	100%	100%	100%	100%	X	X	X	X	X	X	X	X	X	X
Surveys sent to project clients (100%)	0%	61%	0%	0%	0%	100%	0%	100%	100%	x	X	X	X	X	X
Surveys sent to service clients (100%)	91,50%	0%	88,30%	70,24%	20,93%	46,2%	0%	X	X	X	X	X	X	X	X
Surveys: overall score (≥7)	96%	100%	95,6%	100%	100%	100%	100%	100%	100%	100%	100%	62,5% (≥8)	100% (≥8)	100% (≥8)	100% (≥8)
Surveys: technical quality (≥7)	100%	100%	95,5%	94,74%	100%	100%	100%	100%	100%	100%	100%	62,5% (≥8)	X	X	X
Surveys: documentation quality (≥7)	96%	96%	100%	97,37%	100%	100%	100%	100%	100%	100%	100%	50% (≥8)	X	X	X
Surveys: treatment with personnel (≥7)	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	87,5% (≥8)	X	X	X
Overall score survey (≥7,5)	96%	100%	97,5%	100%	100%	100%	100%	100%	100%	100%	100%	70,6% (≥8,5)	X	X	X
Clients that would hire services again	100%	100%	X	X	X	X	X	X	X	X	X	X	X	X	X
New projects (≥3/year)	333%	267%	178,46%	233,33%	33,33% (≥6/year)	183,33% (≥6/year)	166,7% (≥6/year)	133,3% (≥6/year)	50% (≥6/year)	150% (≥6/year)	33,3% (≥9/year)	216,7% (≥6/year)	100% (≥6/year)	120% (≥10/year)	70% (≥10/year)
New services (>65/any)	132%	158%	100%	161,54%	132,31%	172,3%	195,4%	156,9%	176,9%	146,1%	130% (>60/year)	136% (>50/year)	270% (>20/year)	310% (≥20/year)	120% (≥20/year)
Project meetings with TD (11/any)	X	100%	100%	100%	100%	100%	100%	100%	100%	100%	72,7%	100%	X	X	X

INDICATOR (2022 objective)	**2022**	**2020-21**	**2019**	**2018**	**2017**	**2016**	**2015**	**2014**	**2013**	**2012**	**2011**	**2010**	**2009**	**2008**	**2007**
New equipment (5/year)	340%	500%	Inc.869	120%	60%	X	X	150% (>2/year)	200% (>2/year)	100% (>2/year)	120% (>5/year)	140% (>5/year)	160% (>5/year)	X	X
Timing of deviations (under 60 days between planned and real resolution date for 80% of deviations or more) *(figure 4)*	95,3%	73%	100%	96,97%	98,40%	96,15%	88%	83%	68%	58%	63%	81%	60%	X	X
Optimization of documentation management by galenic development (4 activities/year)	225%	25%	200%	50%	275%	100%	X	X	X	X	X	X	X	X	X
Self-inspections to PD and QC (2 actions per department per year)	150%	50% + 100%	X	X	X	X	X	X	X	X	X	X	X	X	X
Internal training of the entire personnel (1 bimonthly)	750%	75%	160%	45,45% (1/month)	100% (1/month)	X	X	X	X	X	X	X	X	10	X
Improvement and control of maintenance actions (>65/year)	166%	107%	66,15%	96,92%	116,92%	1850% (>4/year)	1800% (>6/year)	1483% (>6/year)	X	X	X	X	X	X	X
Validated Excel documents	X	X	X	X	X	Inc730	2	0	0	1	X	X	X	X	X
Compliance actions to cGMP by CQ	N.D.	N.D.	X	X	X	X	0	0	3	4 (dev.)	5	0	X	X	X

ANNEX 2: Acceptance e-mail to present a poster at the 41st AEFI symposium in 2023

(AEFI: *Asociación Española de Farmacéuticos de la Industria* or Spanish Association of Industry Pharmacists)

SM

Sandra Módenes <secretariatecnica.catalana@aefi.org>
Per a: JÚLIA PRATS I VALLÈS

Dl. 8/5/2023 10:37

Buenos días, Julia:

El resumen ha sido revisado y aceptado.

Le esperamos en el 41 symposium de AEFI.

Saludos cordiales,

SANDRA MÓDENES
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ASOCIACIÓN ESPAÑOLA DE FARMACÉUTICOS DE LA INDUSTRIA (A.E.F.I.)
PROFESIONALIDAD, INTERRELACIÓN, COMPROMISO

ANNEX 3: Poster presented at the 41st AEFI' symposium, 6-7th of June 2023, Barcelona.

INDICADORES DE CALIDAD EN UNA PLANTA PILOTO

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INTRODUCCIÓN

- Optimización del conjunto de indicadores de calidad y su medida mediante la revisión anual.
- Proponer un conjunto de indicadores a implementar en la nueva planta piloto UB-Farmatec de acuerdo con las normativas actuales referentes a los indicadores de calidad.

METODOLOGÍA

1. Se analizaron las normas de calidad relacionadas con la industria farmacéutica sobre la presentación de datos de los indicadores de calidad.
2. Se realizó una compilación histórica de 2009 a 2022 de los indicadores de calidad en uso en el SDM (Servicio de Desarrollo del Medicamento) y se analizó su idoneidad y posible uso en la planta UB-Farmatec.

RESULTADOS

	ISO 9001:2015	NCF	ICH Q10	Guía de la FDA
Objetivos de calidad	✓	-	✓	-
Cuadro de indicadores	✓	✓	✓	✓
Registro de incidencias y CAPA	✓	✓	-	-
Gestión de incidencias y reclamaciones	✓	-	-	✓
Identificación de oportunidades de mejora	-	✓	✓	-
Revisión periódica del sistema de calidad	-	✓	✓	-

Tabla 1. Requisitos de las normativas referentes a la gestión de la calidad respecto al uso de indicadores de calidad.

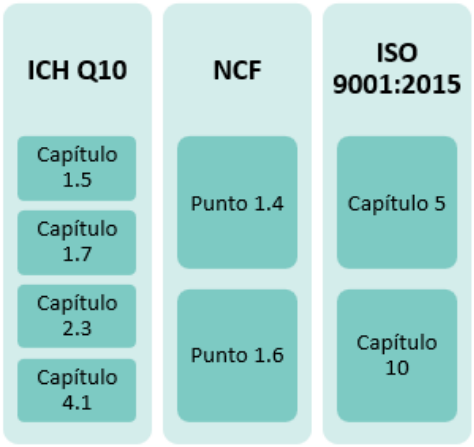

Figura 1. Apartados de las normativas donde se referencia el uso de los indicadores de calidad.

Nº IND	INDICADOR	DEPARTAMENTO RESPONSABLE	CUANTIFICACIÓN	OBJETIVO	NORMA RELACIONADA	CÓDIGO FICHA
1	Reuniones de calidad	DT y UGQ	Σ reuniones	1/mes	ISO 9001 NCF ICH Q10	001
2	*Timing* cierre incidencias	UGQ	Días entre cierre previsto y real	≤60 días	ISO 9001 ICHQ10	002
3	Número de proyectos nuevos	Producción	Σ proyectos	2/año	ISO 9001	003
4	Valoración de los clientes	DT	Valoración encuestas	>7 en todos apartados	ISO 9001 ICH Q10	004
5	Número de autoinspecciones	DT y UGQ	Σ autoinspecciones	3/año	ISO 9001 NCF	005

Tabla 2. Propuesta de indicadores para UB-Farmatec.

CONCLUSIONES

El análisis de los indicadores del SDM desde 2009 ha facilitado la identificación de los indicadores clave para la valorización de los procesos. Se han seleccionado cinco de ellos para la nueva planta piloto UB-Farmatec.