MASTER IN BIOMEDECINE

How to implement a Quality Management System in an European pharmaceutical company in compliance with GLP, GCP and GMP/GDP guidelines

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Award date:
2022

Awarding institution:
University of Namur

UNIVERSITÀ DEGLI STUDI DEL PIEMONTE ORIENTALE
"AMEDEO AVOGADRO"

DIPARTIMENTO DI SCIENZE DEL FARMACO

EMOTION

The European Master in Translational Cosmetic and Dermatological Sciences

Thesis:

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Declaration of Authenticity

I, LEIRE LARRAÑAGA enrolled in the European Master in Translational Cosmetic and Dermatological Sciences at Dipartimento di Scienze del Farmaco (EMOTION), Università del Piemonte Orientale (UPO) and discussing the Thesis in September 2022 (extraordinary session)

declare that

- This thesis is my own original work, based on my personal study, experience and/or research.
- I have acknowledged all material and sources used in its preparation (*e.g.* books, articles, reports, lecture notes, and any other documents, including websites or personal communications).
- I am aware that false statements will be punished by law (art. 76 del D.P.R. 28.12.200 n.445).

Date 29-08-2022 Signature

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ABSTRACT

Drug development is a significant and expensive challenge. Pharmaceuticals are lengthy, high-risk businesses committed to discovering and developing innovative, efficacious, and safe new products. The drug discovery and development process, from early development until product approval and commercialization, generally takes approximately 15 years with an average cost of 985 million of euros. Every pharmaceutical industry focuses on maintaining quality throughout the overall research and development process because quality can control other essential factors such as safety and efficacy and can decrease the cost for developing a new product. Moreover, the pharmaceutical industry is the most regulated one in the world. In the European Union, new innovative medicines can only be commercialized if they have previously received specific authorization from the competent national authorities or European Commission. So thus, quality is the most vital aspect of medicinal products and the pharmaceutical industry. A team of quality experts within a pharmaceutical company are included in the Quality Assurance (QA) department and their goal is to achieve quality through the implementation of the Quality Management System (QMS). Furthermore, a well-defined Quality Documentation System (QDS) is the base of a successful QMS. An innovative characteristic of QMS new modern approaches in the health care industry is that the quality requirements are directly imposed on the company's management system and not the product. It has also been proved that different parts of a QMS can be integrated into a single QMS using standard elements, defined as Integrated Quality Management System (IQMS). The organizational structure of the host organization where the internship has developed was used as a reference point for the description of the proposed QMS for a pharmaceutical company. The ideas described are in compliance with regulatory requirements within EU and GxP guidelines. A strictly structured Documentation System and Organizational Quality chart are the strength points of a QMS, and both are reflected in this report. The information provided related to the documentation management by specific examples and procedures is considered an important aspect of the report as the ideas are developed not only in a theoretical but also in a practical way. Additionally, the idea developed thorough this report is related to a simple and specific pharmaceutical organization. So thus, the idea is considered limited in some aspects. As a final conclusion, there is not any general QMS that could be valid for all the healthcare industries but the information described in this report could be used as a partition point for the implementation of an Integrated QMS in different organizations and pharmaceutical profiles.

KEY WORDS: Pharmaceutical, Quality System, GxP, Documentation, Organization

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THE HOST ORGANIZATION [1]

The host organization where the creation of this report started is called Nerviano Medical Sciences S.r.l.(Nervianoms). Nervianoms is a successful Italian pharma company engaged in the discovery and clinical development of small innovative molecules for oncology. It combines the flexibility of a biotech with the quality of a big pharma to bring the best-personalized medicines to cancer patients. The company takes innovative approaches to drug targets and novel mechanisms of action to develop new therapy opportunities and to generate effective and selective molecules. It presents a strong commitment to collaboration with academia and clinical investigators as well as with industrial partners worldwide to fulfil the programs from early drug discovery to clinical development. In Nervianoms S.r.L 130 experts work every day to develop the first in class pharmaceutical products with a strong base in Good Clinical Practices (GCP). Moreover, Nervianoms is able to cover the whole range of additional aspects of drug development, such as preclinical studies and manufacturing and distribution through Accelera and NerPharma affiliate companies.

Accelera is an Italian company committed to experimentation and preclinical research. It is a promising Contract Research Organization (CRO) working and collaborating with different biotechnology and pharmaceutical companies worldwide with a solid Good Clinical Practice (GLP) base. Furthermore, NerPharma is a Contract Development and Manufacturing Organization (CDMO) engaged with developing and manufacturing products from the formulation of the active ingredients up to packaging. With a wide range of Good Manufacturing Practices (GMP) services, NerPharma has brought new products and unique technologies to the market over the years.

The three subsidiary companies, Nervianoms, Accelera and Nerpharma, work parallelly within the management and control of a high-level coordination team called NMS Group (Figure 1). NMS group is composed of highly qualified pharmaceutical industry experts and is considered the largest Italian pharmaceutical company. NMS Group is able to manage the overall integrated R&D chain within the oncology field through the three subsidiary companies. It has a strong mission of improving patients' health through a strong commitment to discover, develop and deliver life-changing molecules. Nervianoms is considered the innovative core of the high-level NMS group pharma company.

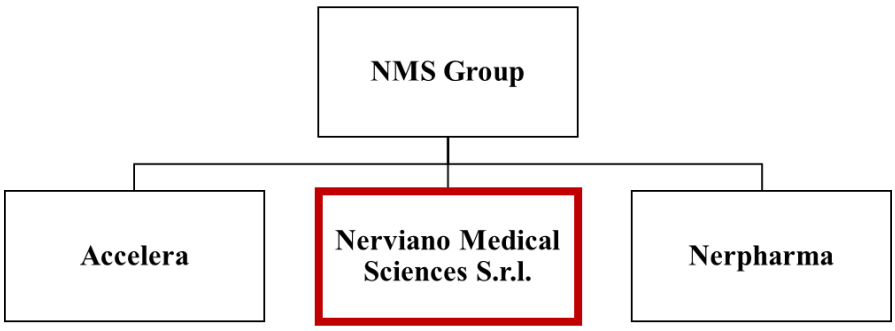

Figure 1: General schema of the organization from the host institution: Nerviano Medical Sciences S.r.l

Each subsidiary company is firmly committed to commercializing the best quality pharmaceutical innovative products. So thus, each company has implemented a Quality Assurance Team within the company responsible for supervising every step involved in the drug R&D process, ensuring the safety, efficacy and quality of the process and the final drug product.

1. INTRODUCTION

Drug development is a significant and expensive challenge. Pharmaceuticals are lengthy, high-risk businesses committed to discovering and developing innovative, efficacious, and safe new products [2]. The drug discovery and development process, from early development until product approval and commercialization, generally takes approximately 15 years. Furthermore, the average cost to bring a new innovative drug to market is 985 million of euros [3]. There are not quantified average failure costs expended during a pharmaceutical product's life-cycle development but it is known that they are relatively high compared to preventive and appraisal costs (Figure 2). So thus, in the last decades, there has been a growing awareness of improving the quality of the pharmaceutical development processes [4].

Three key factors determine whether any pharmaceutical industry will succeed: Efficacy, safety, and quality [5,6]. In many pharmaceutical markets, quality competition is perceived as somehow being equally important to price competition, and this trend is only expected to continue. Basically, commercially viable trading is expected to depend on Quality Assurance best practices within the pharmaceutical company [7].

Every pharmaceutical industry focuses on maintaining quality throughout the overall research and development process because quality can control other essential factors such as safety and efficacy. Although the primary purpose of all health care industries is to produce zero defect products, there are many challenges or failures in obtaining it. The implementation of total Quality Management has become very important in the pharmaceutical industry in order to try to achieve zero defects in the drug development processes. As the quality level rises, the Total Cost of Quality (CoQ) during the development process falls. So thus, the implementation of a predefined Quality System will not only be useful for achieving a high-quality drug product but will also be more economical (Figure 2) [5].

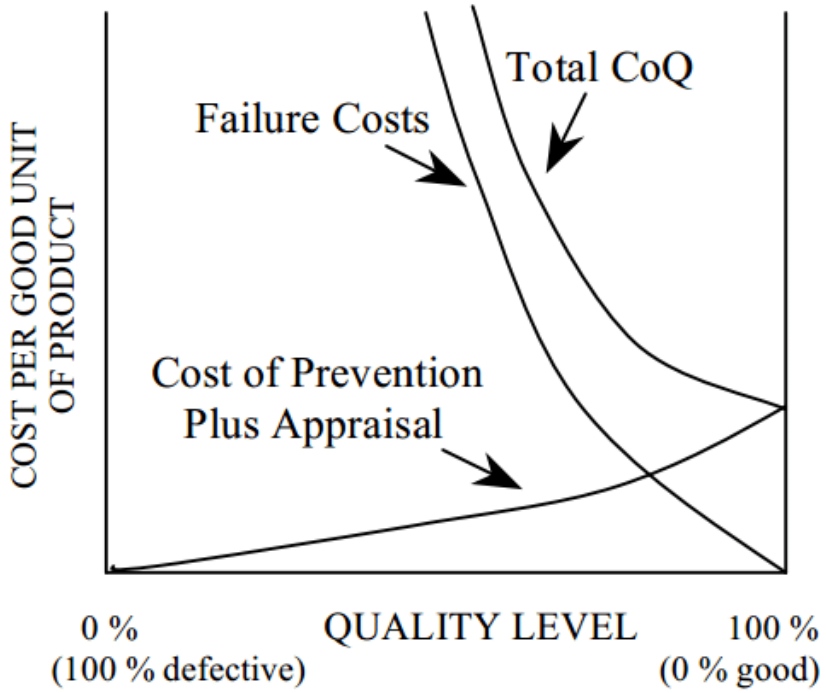

Figure 2: Cost of development of new medicinal products vs. the Quality level [8]

The earliest research, synthesis and design of one or more promising molecules, informed by well-executed and well-designed nonclinical and clinical studies and with a well-controlled manufacturing process need to be prepared for a submission package for regulatory approval. The regulatory environment around the pharmaceutical industry has become more stringent in the last decade, leading to new and more demanding hurdles that a new innovative drug must clear to commercialize [9]. Due to this fact, preparing a development plan in the earliest stages has become an essential aspect in order to ensure that proposed studies will satisfy the regulatory requirements [10].

Moreover, the pharmaceutical industry is considered the most regulated industry in the world [2,11]. In the European Union, new innovative drugs can only be commercialized if they have previously received specific authorization from the competent national authorities or European Commission [12]. So thus, companies have different options to obtain the approval of new pharmaceutical products: by a centralized procedure through the European Medicine Agency (EMA) (EU level), by a decentralized procedure with a specific country's competent authority or via mutual recognition. It depends on the profile and characteristics of the new medicine the correct commercialization pathway [13].

Different guidelines are published in order to facilitate the companies' regulatory approval package process. Directive 2001/83/EC is responsible for addressing the applications submitted to EMA for the new medicinal product approval. Additionally, The Committee for Human Medicinal Products (CHMP) it is essential in the authorization process of medicines as it conducts initial specific assessments for marketing authorization applications within EU [13].

What is more, The International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use was initiated in 1990 and is a strong project that converge the regulatory authorities of Europe, the United States and Japan and experts from the health care industry in the mentioned three regions. The main goal of such harmonization is to discuss the up-to-date scientific and technical aspects of product registration, to abolish any step that is not relevant through the global development and to use animal, material, and human resources more efficiently. In the beginning, ICH imposed that Safety, Quality and Efficacy are the main criteria of any new drug product approval. With time, ICH mission has continued to involve different aspects of the pharmaceutical industry, creating innovative guidelines that every health care industry must comply in order to satisfy regulatory requirements [14]. The major goal of the ICH also includes maintaining protections for quality, safety, regulatory requirements, efficacy, and public health [15]. ICH guidelines have helped the industry to avoid repetition in testing or reporting, it has reduced development times, saved resources and benefited the patient [14].

Different ICH guidelines are described through the overall pharmaceutical development process (Figure 3). Preclinical and research studies are conducted in compliance with Good Laboratory Practice (GLP) guidelines. However, Good Clinical Practices (GCP) criteria being global quality and safety requirements for the design, execution, and reporting of clinical studies, are closely followed when conducting clinical trials. GCP compliance safeguards the rights and safety of clinical trial participants, hence it is crucial. Finally, drug manufacturing and distribution is conducted according to Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP). All the above-mentioned guidelines compliance are subject to regulatory inspection [2,5].

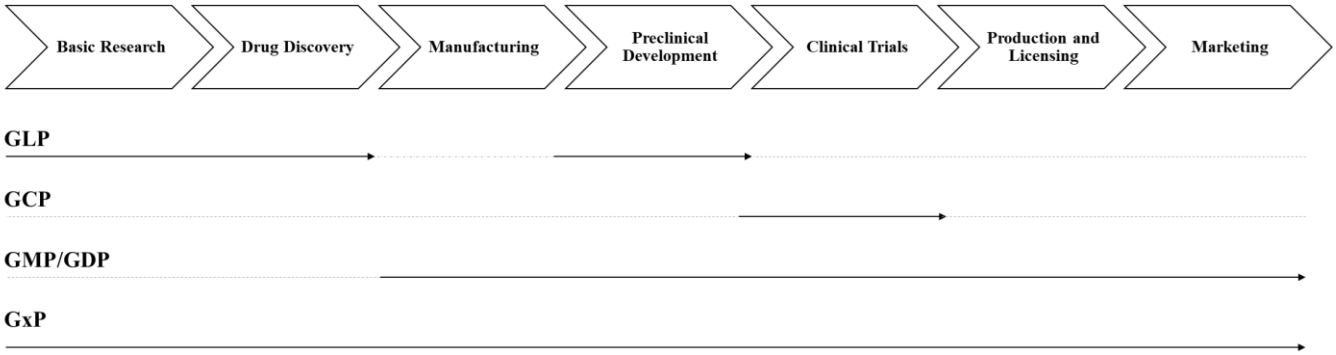

Figure 3: Pharma product development process with the correspondent GxP guidelines for each step

So thus, quality is the most vital aspect of medicinal products and the pharmaceutical industry. Once the medicinal product is in the market, there is no scope to rectify the defects at the users' end, so it is essential to evaluate the quality of the pharmaceutical product during its life-cycle development (Figure 3) [6].

A pharmaceutical quality professional is responsible for evaluating the product from its earliest research to patient delivery. Ideally, the medicinal products should be appropriately designed and monitored during the entire development process and care should be taken during the manufacturing and distribution process to protect the quality attributes. Quality Risk Management (QRM) and Quality By Design (QbD) are popular techniques used to ensure the effectiveness of the implemented QMS. Standard Operating Procedures (SOP) and adequate training to professionals directly involved in the development process are key aspects of delivering high-quality products. The pharmaceutical business should possess a holistic approach during the development process and quality experts must be responsible for implementing and monitoring the mentioned aspects [6]. A team of quality experts within a pharmaceutical company are included in the Quality Assurance (QA) department and their goal is to achieve quality goals through the implementation of the Quality Management System (QMS) [4].

Up to date, the pharmaceutical companies have made huge progress toward implementing and certifying QMS. A well-defined QMS combines human resources, process inputs, interrelated processes and outcomes always monitored by continuous improvement programs. Through a successful QMS, quality objectives can be systematically defined. Quality must be linked to the company's strategic goals and directly implemented into the organizational processes and structure. An essential aspect of a QMS within the pharmaceutical industry is to share responsibility for quality transversally across the organization and to drive a general culture that recognizes the importance of quality through the company overall [16]. QMS is a process designed to provide a predictable and high level of product quality and development process. QMS in health care industries within European Union are implemented following GLP, GCP, GMP/GDP and ISO 9000 International Standards (IS) [16].

An innovative characteristic of QMS new modern approaches in the health care industry is that the quality requirements are directly imposed on the company's management system and not the product. It has also been proved that different parts of a QMS can be integrated into a single QMS using standard elements, defined as Integrated Quality Management System (IQMS). The IQMS can facilitate aspects such as planning, resources, the definition of complementary objectives, and monitoring and evaluating of the organization's overall performance. The principal objective when

arranging an IQMS is the creation of joint well-documented subsystems for Quality Management as well as their arrangement in terms of corporate management of the enterprise [17]. However, in some cases in order to meet regulatory requirements, pharma companies are forced to implement several QMS within the same company. The definition of IQMS was adopted due to the development of systems harmonizing several International Standard Requirements, such as GxP guidelines [18]. Integration has become a natural stage of QMS all over the globe, creating innovative opportunities for the development of organizations. Generally talking, the arrangement of an IQMS is a labour-consuming, innovative project aimed to improve the performance of the old-fashioned Quality Systems. IQMS provides an increase in the effectiveness of the standard structure of the Documentation Management System [17].

Concise and clear documentation is necessary to manage all the issues in the healthcare industry. Approval requests for a new medicine must be based on the clear documentation described during the product development process. Furthermore, a well-defined Quality Documentation System (QDS) is the base of a successful QMS. The processes involved in developing new medicines must be standardized, monitored and appropriately archived. Without a Good Documentation Practice (GDP) culture and knowledge established within the pharma company, a new drug product will never obtain commercialization approval. So thus, pharmaceutical companies stablish standard documentation systems not only to ensure the quality of their final product but also to obtain the highly desired regulatory approval. Furthermore, the most common inspection findings during auditing is a lack of adequate, reliable and accurate source documentation, so an up-to-date documentation system has become one of the most controlled aspects of the healthcare industry [19,20].

Documentation is controlled and managed in almost every pharma company by documentation hierarchy system. Different researches have shown that hierarchy methodology improves usability, management and user satisfaction within the companies. Furthermore, hierarchical structures identify the independence and dependence relationships of the different aspects and steps and is able to provide a clear valuable information. In general terms, hierarchical structures allows the easy representation and fast learning of the documentation system implemented within the company. Divide and conquer techniques are greatly aided by hierarchical documentation systems, which even enhance accuracy and effectiveness [21].

Every pharmaceutical company, from the simplest to the most complicated, must have a well-described organizational structure on which to operate. The principal purpose of establishing a strictly defined organizational structure within a company is to achieve effective and efficient results, increasing the corporate's growth. The success and growth of a pharma company depend on how well an organization and performance are structured and how well the roles and responsibilities of all the people involved in the company are defined. An organizational organigram is a powerful tool to demonstrate the company's solid organizational structure. Furthermore, it is generally known that any organization's structure must be based on its goals and specific properties. Pharmaceutical companies define strict quality organizational structures to ensure the company's compliance with producing safe, efficacious and high-quality medicinal products [22].

2. MATERIALS AND METHODS

A deep search was done on the following databases: ICH, FDA, EMA, WHO and Eudralex. Using Google Academy, PubMed and ScienceDirect a considerable number of papers and articles were downloaded and studied to better understanding of the topic and to enrich the described report. Topics such as pharmaceutical Quality, Quality Management Systems and Good Documentation Practices in a pharmaceutical company were highly investigated. Articles and papers with no academic nature were rejected during the search to ensure the report's truthfulness. A huge documentation investigation was made around the ICH GLP, GCP, GMP and GDP guidelines, which are directly related to this report. International Standards of the pharmaceutical industry and Quality Management System in a pharmaceutical company are the themes that could be identified as the most studied ones to write this report.

Pharmaceutical companies with an Integrated Quality Management System thorough all the pharmaceutical product life-cycle were investigated in Google search to understand the quality structure of different Pharmaceutical Organizations. Documentation systems used in pharmaceutical companies have been also investigated in order to make the best purpose through this report.

The organizational structure of the host organization where the internship has developed was used as a reference point for the creation of this report. However, it is not described any real information from the company's current Quality Management System. Meetings with expertise in GLP, GCP, and GMP/GDP were organized to ensure the information related in this report during the internship in the host organization. Comparison and investigation of the host organization documentation was done to develop this project. Corrections by quality pharmaceutical experts have been done in order to ensure the correctness of the described information. The information and the proposed ideas described throughout this report have been ensured to comply with GxP guidelines of a pharmaceutical company.

3. RESULTS

A Pharmaceutical Company able to develop the entire life-cycle of a medicinal product, from the earliest drug research up to the commercialization, can be organized by different organizational organigrams and structures. The existing possibilities are infinite, and the specific and different organizations are based on their unique properties and scope. This report uses simplified and general organization schemas described below as a reference point (Figure 4 and 5).

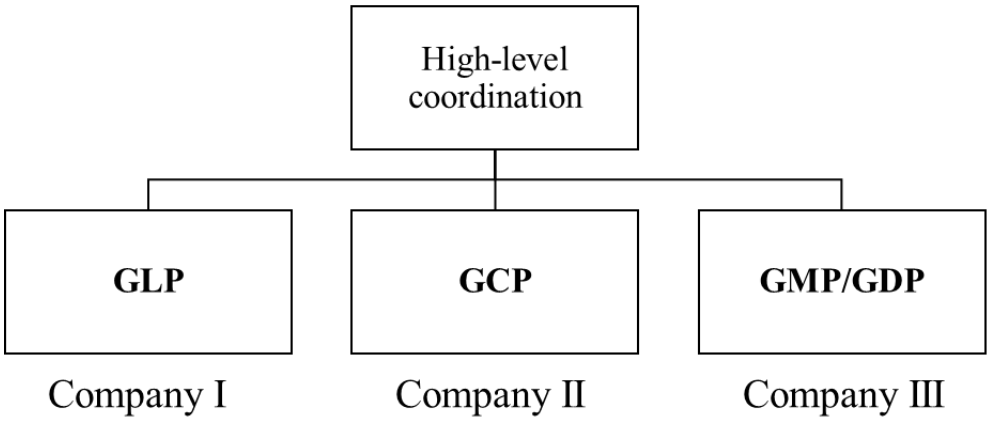

Figure 4: Schema of a company able to develop all the life cycle development of pharma product by collaboration of different companies within same high level corporate. Each company is focused in different steps of the pharmaceutical development: Company I: Laboratory and Preclinical research (GLP), Company II: Clinical Research (GCP) and Company III: Manufacturing and Distribution (GMP/GDP)

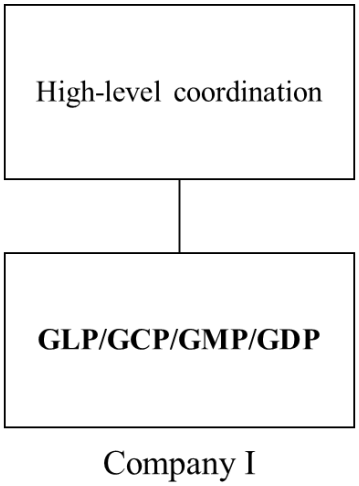

Figure 5: Schema of a pharmaceutical company able to develop within the company all the life cycle of pharma product: Laboratory and preclinical research, clinical research and manufacturing and distribution

The Quality Management System described below is based on these defined organizational structures. However, the information and ideas described thorough the document can be extrapolated to further structures.

3.1. DOCUMENTATION

The base of a well-organized, effective and compliant with regulatory authorities pharmaceutical QMS is a well-defined Quality Documentation System. Documentation must be organized, standardized and strictly controlled during all the drug research and development process. Hierarchical documentation methodology is considered to be the best approach for those IQMS established within a pharmaceutical company that supervises the entire process. Documentation system must be defined in compliance with GLP, GCP, GMP and GDP guidelines. The word "Global" is written through this report and it is used as synonym of "Integrated" or "Overall". QMS and IQMS are considered synonyms too.

3.1.1. Documentation hierarchy

The proposed documentation hierarchy for an Integrated Quality Management System is described in the following figure:

Figure 6: Documentation hierarchy in a Global QMS

Quality Manual:
Quality Manual is the highest level governing document inside the Quality Documentation System and is used to describe the overall QMS defined in the pharma company. Inside the Quality Manual, the scope, purpose, linkages, and independencies of the implemented QMS must be clearly defined and compliant with GxP guidelines, and it must be used as a governing document for all the documents described inside the company. The points described below must be strictly followed to ensure an efficient Integrated QMS:

- Quality Manual is the governing document of the Quality Documentation System within the QMS, so all the staff directly involved in the R&D process within the pharma company must work in compliance with the described document
- Quality Manual must comply with all the regulatory requirements throughout the pharmaceutical product life-cycle. Moreover, it must be described in compliance with GxP guidelines
- All the guidelines that are used as source documents inside the company must be clearly mentioned in the Quality Manual
- The quality organization structure of the company must be clearly described in the Quality Manual
- The IQMS must be clearly described and all the responsibilities for the personnel directly involved with quality must be defined within this document
- If the Quality Manual is changed or actualized, all the documents inside the company must be revised to see if the change has impacted their content. If yes, they should be changed as soon as possible. If no, they should justify the reason
- The document's extent depends on how many aspects must be included. Quality Manual is considered a general reference that describes all the aspects of the QMS inside the company. The established Quality System must be included, mentioned and explained.
- The Quality Policy must be included inside the Quality Manual. The Quality Policy must describe the company's compliance with the quality and explain how this compliance is achieved. The Quality Policy must also include the overall expectations that the company's personnel must fulfil to comply with the regulatory authorities and the company's requirements. Quality policy is used to demonstrate the quality culture within the pharma company

Global Standard Operating Procedures (GSOP):

Global Standard Operating Procedures (GSOPs) give instructions for performing transversal operations across all or more than one different phase of the product's life-cycle within the company. GSOP documents can be directly used at the local-phase level or cascaded in a phase-specific document if necessary (Figure 9). The following points must be taken into consideration within the implementation of the QMS:

- All GSOPs must comply strictly with the information described in the Quality Manual
- Apart from Quality Manual, no governing document has the power to influence the GSOP described inside the company
- GSOP must only describe transversal processes across the product life-cycle OR at least through more than one different phase within the product life-cycle, including more than one GxP Guidelines (GLP, GCP, GMP or GDP). It must be clearly defined in all the GSOPs to which phases the document is related to
- GSOP can be directly applicable to each specific phase of the process. If more specifications are needed due to phase-specific regulatory requirements, GSOP can be cascaded to different specific procedures (ex, SOPs)
- GSOP is considered the governing document of all the documents described in specific process phases, and these documents must mention the GSOP, with which they are compliant.

Phase-specific Policies and Standard Operating Procedures (SOPs):

Phase-specific documents give the instructions for performing operations specific to a unique phase of the entire process in compliance with JUST one GxP Guideline. There are some specific processes that must be described by specific procedures such as SOPs and Policies as competent authorities require. Points to strictly consider when describing phase specific documents:

- All the described SOP and Policies must be compliant with the Quality Manual described within the company and, if applicable, with the specific GSOP they are related to
- It must be ensured that a cascade of a described GSOP is necessary before creating a specific SOP or Policy. If not, GSOP can be directly applied
- SOPs and Policies must be specific to a single guideline (GLP, GCP, GMP/GDP) and a unique phase. In the case that the specific procedure is related to more than one guideline or phase, it must be defined as GSOP
- SOPs and Policies must follow the same structure through all the phases, through a Global template. If necessary, changes can be made, always with a justified reason.
- It must be clearly described to which phase and process is directed the described SOP and Policy

3.2. QUALITY ORGANIZATIONAL CHART

A well-defined Quality Management System must be controlled and managed by a strictly described organizational structure, where the job positions and responsibilities are clearly defined. A Quality Organizational structure must be established and maintained to ensure that services and products of the company satisfy applicable regulations, company and customer expectations. Following, described organizational charts are based on the structure of the pharmaceutical company that has been defined above (Figure 4,5).

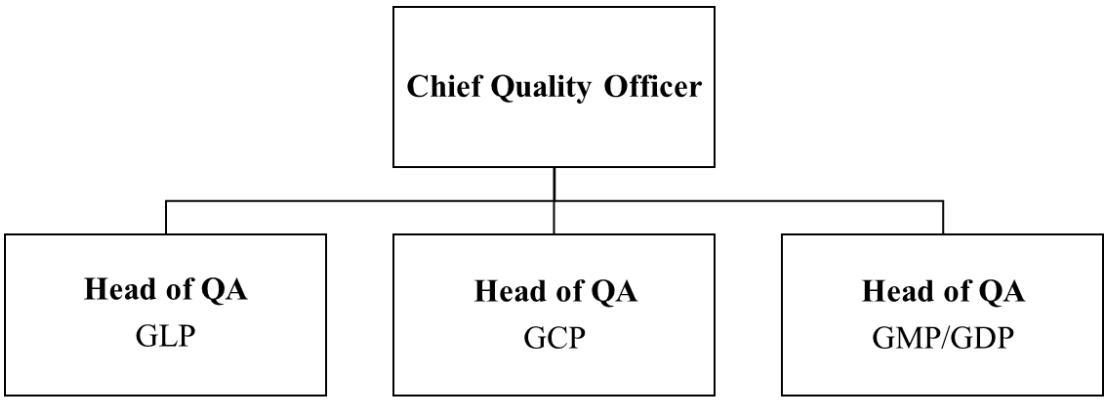

Figure 7: Quality Organizational Chart for the implementation of QMS for the company structure defined in Figure 4

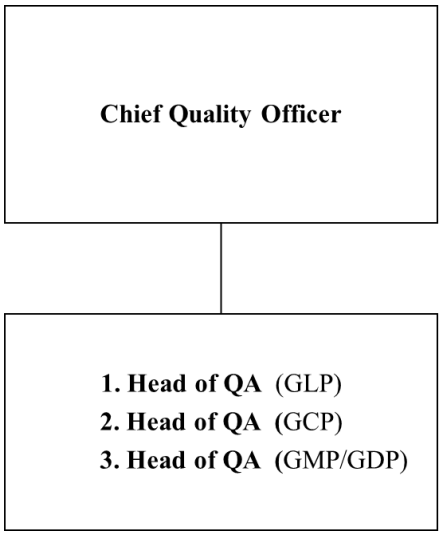

Figure 8: Quality Organizational Chart for the implementation of QMS for the company structure defined in Figure 5

Chief Quality Officer
Chief Quality Officer (CQO) is the highest level position related to the Quality Management System, so it is considered the highest responsible of the quality system. o The CQO is in charge of the QMS' overall efficacy and has the greatest level of authority in the quality field o CQO is the owner of the Quality Manual and GSOP within the pharmaceutical company o It can be responsible for developing Internal Audits through the different phases of the process. If another figure does it, CQO must be involved in the process o CQO manages and controls all the Global aspects related to Quality and must control the scaling different job responsibilities within QMS o CQO must be the link between the different Head of QA within the pharma company o The CQO ensures that responsibilities, roles, and authorities related to the QMS are defined and that timely and effective communication is developed o CQO will achieve escalation within all the levels of management in case of quality issues
Head of QA
A Head of QA must be defined for each phase of the pharmaceutical product development, and the responsibilities are separated based on the guidelines: GLP, GCP and GMP/GDP. So a Head of QA must be appointed to define, manage, control and implement the Quality Systems of the specific phases and to guarantee compliance with applicable regulatory requirements and high level GxP documents described within the company. o Each Head of QA is responsible of the compliance and management of the QMS within the specific phase o Head of QA is the owner of the specific SOPs and Policies described within the phase o The Head of QA reports directly to the CQO in order to ensure the efficacy of the QMS thorough all the processes

- Head of QA supervises a qualified QA Team that will be directly involved in all the issues related to the QMS
- Head of QA is responsible for investigating the impact of the phase-specific procedures if a change is done in a governing document (Quality Manual and, if applicable, GSOP).
- Head of QA is directly involved with the personnel working in the specific phase and it is the responsible to implement a good quality mindset within the process
- Head of QA is responsible of organizing, monitoring and tracking the GxP training to all the staff directly involved with regulated processes.

3.3. QUALITY MANAGEMENT SYSTEM

The high-level coordination is responsible to ensure and demonstrate a strong and visible commitment to Quality within the company. All the aspects of the Research and Development process must be standardized and controlled by a personalized and dedicated document. The Integrated Quality Documents must be aligned with the overall product life-cycle processes covering GxP regulated activities.

3.3.1. Implementation of documentation and ownership

Each document described within a pharma company must have a specific purpose and scope defined. Each document is directed to a specific phase/phases of the process and the objectives of the document must be clearly described. Following there is shown how is implemented the defined Documentation Hierarchical System directly to the pharmaceutical lifecycle process.

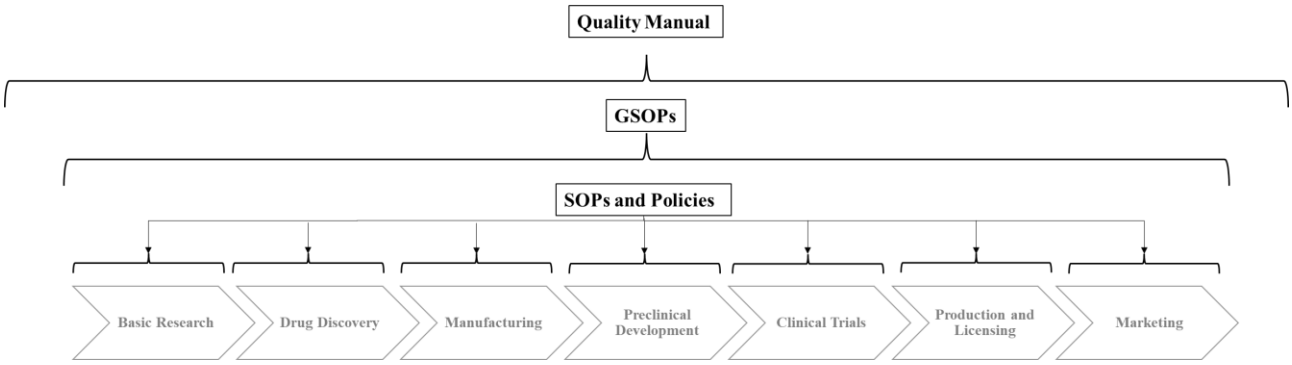

Figure 9: Schema of how is implemented the Quality Documentation System thorough the life-cycle of the pharma product. *GSOPs are not always directed to all the process

Moreover, all documents need to be managed, monitored and controlled. The appropriate responsibility and authority must be established for each document. Each document must have an owner defined. Depending the level of the document the owner is different. The owner has the total responsibility of the documents that are within its authority and must ensure the compliance of all of them and monitor them until its archival. Following there are defined the owner for the above defined Documentation system:

DOCUMENT TYPE	OWNER
Quality Manual	CQO
GSOP	CQO
SOPs	Head of QA
Policies	Head of QA
Document Templates	CQO

Table 1: Documents owner

It is important to define a standard Document ID to each document described within the Quality Documentation System. The Document ID must be alpha-numeric and it must follow different rules:

DOCUMENT TYPE	DOCUMENT ID
Quality Manual	QM-XX-YYYY
Global Standard Operating Procedure	GSOP-XX-YYYY
Phase specific Policies	Pol-XX-YYYY
Standard Operating Procedures	SOP-XX-YYYY
Templates	Temp-XX-YYYY

Table 2: Document ID generation

- **XX number:** It is directly related to the specific department/aspect/phase of the process (if necessary)
- **YYYY number:** It is the number that will be increasing depending the quantity of documents described. It is a sequential number. Ex: First document described in a specific phase: SOP-XX-0001

This information must be developed in the SOP on SOP that each specific company/phase (GLP, GCP and GMP/GDP) must describe within the company in compliance with their applicated regulation. Each company/phase need to have an specific governing document within their authority.

3.3.2. Mandatory specific SOPs and Policies

The documentation management must be included in all the phases and levels inside a pharma company. Moreover, some processes need a specific Standardized Quality Document based on the applicable regulatory requirements for each phase and must preserve a primary purpose on their creation (Figure 10). Each SOP must have a specific objective and must comply the Quality Manual and if applicable with the GSOP described in the pharmaceutical company. Specific procedures (SOPs and Policies) are mandatory to be described in the following areas:

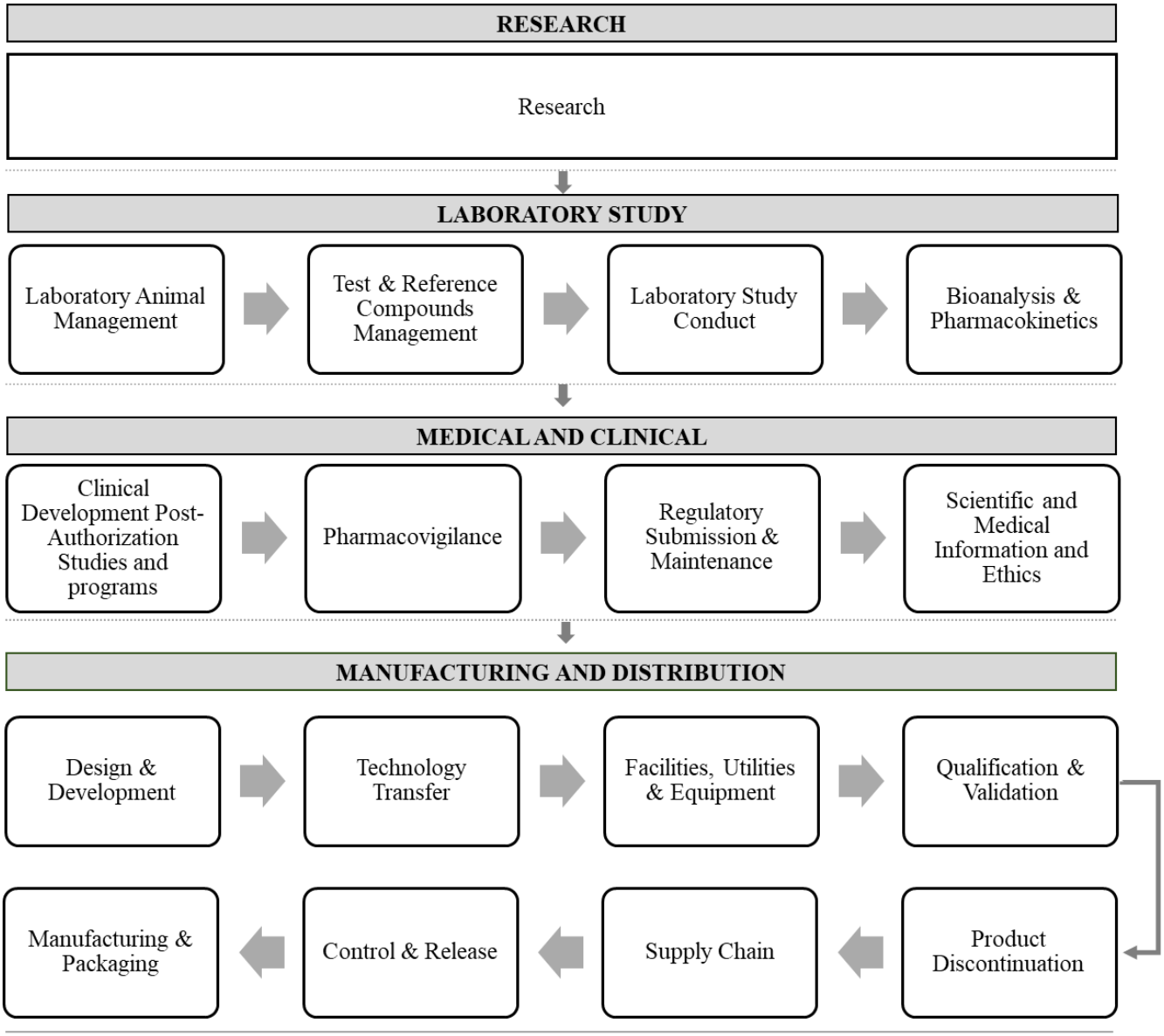

Figure 10: Specific steps of the pharma product life-cycle that must be specifically documented by specific Standard Documents

Research Process

- Research:

Although it is a process not covered by GxP, it must be included in the Global Quality Documentation system and standardized to ensure that the first stages of product development, including basic scientific research and drug discovery, are efficiently performed, organized, and organized documented and archived.

Laboratory Study Process (GLP guidelines):

- Laboratory Animal Management:

To ensure compliance with the fundamental principles of animal welfare. Animal welfare is a strictly regularized process and all the management of all the aspects related to the care and use of laboratory animals must be documented

- Test & Reference Compounds Management:

All the articles that are the subject of a laboratory study or provide a basis of comparison with the study subject must be managed by standardized documentation

- Laboratory Study Conduct:

To ensure the efficient management of laboratory studies such as the protocol, the generation of study data, the production of the report and data archiving. Essential to ensure compliance with GLP guidelines for the regulatory requirements

- Bioanalysis & Pharmacokinetics:

To demonstrate the efficient management of the biological samples, which provide understanding and knowledge of the disposition of the pharmaceutical products in animals and humans

Medical and Clinical Process (GCP guidelines):

- Clinical Development, Post-Authorization Programs:

To provide necessary knowledge and documentation for product registration and medical and clinical knowledge throughout the product life cycle. GCP guidelines must be strictly followed

- Pharmacovigilance

To ensure the safety profile and contribution to evaluating the therapeutic value of all the products involved in clinical development. It is also necessary to ensure continuous monitoring and management of the safety profile and risk minimization through the benefit-risk assessment throughout the life-cycle of the pharmaceutical products.

- Regulatory Submission & Maintenance:

To manage the necessary regulatory activities required for the Regulatory Authorities application submission.

- Scientific and Medical Information & Ethics:

To ensure and demonstrate the responsible conduct and protection of human rights during the clinical studies and programs. It is also necessary to ensure that scientific and medical information is provided according to International Standards.

Manufacturing and Distribution Process (GMP/GDP guidelines):

- Design & Development:
  To ensure the effectiveness of Quality by Design defining the control strategy suitable to the product quality, strength and purity for its intended purposes. It is also used to ensure that the product and process design and development show effectiveness on the commercial manufacturing routine with its common quality attributes
- Technology transfer:
  To ensure that the transfer of a product is reliable, robust, cost-effective and is done with the appropriate manufacturing, packaging and testing controls, always complying with the applicable regulatory and company requirements

- Facilities, Utilities and Equipment:
  To ensure the high quality of design, management and maintenance of facilities of the studies and minimize the risk of contamination on the facilities, utilities and equipment used for manufacturing and distribution of the products
- Qualification & Validation:
  To demonstrate the compliance of the critical aspects with the pre-established requirements of the development, manufacturing, control and distribution processes
- Manufacturing & Packaging:
  Ensure that the manufacture and package of products always meet all the required specifications and quality attributes
- Control & Release:
  To ensure that intermediates and finished products are sampled, analyzed and formally released in compliance with Quality Management before using or distributing the material
- Supply Chain:
  To ensure the timely delivery of the correct quantity and quality of the materials used in the manufacturing and packaging processes, to manage the physical flows of the materials and products and to ensure when a product is deemed to take proper product discontinuation actions
- Product Discontinuation:
  To manage the issues or activities associated with the terminal stage of the product life-cycle and to develop a continued product assessment and report following the applicable regulatory requirements.

3.3.3. Proposed quality transversal processes for GSOP creation

The transversal processes are defined as the processes that can be transversal through all the phases of the pharmaceutical product development or through more than one phase. Specific GSOP is developed for each transversal process related to GxP and public-health regulations. Following are described the proposed transversal processes based on the GxP guidelines. All the described processes are considered transversal though all or on more than one the pharmaceutical product phase:

- Personnel Qualification and Training

All the employees within a pharmaceutical company who are directly or indirectly operating within the QMS and are engaged in the research, development, manufacturing, distribution and discontinuation of the products and services, must be enough qualified and trained for their assigned roles. Training must be based on the updated applicable regulations and is mandatory for all the employees involved to participate in the specific training directed to the regulations described within their functional areas. Moreover must be developed with enough frequency and monitored in a standardized and controlled way to ensure in case of inspections the high qualification of the employees.

A training high level standard structure must be defined by a GSOP, directly affecting all the process and ensuring the right education, skills, training and experience for all employees. Moreover, in order to ensure the most successful training inside each phase, the GSOP must be cascaded in specific SOPs with the specific details of training for each specific phase. The specific SOP will be written in compliance with the governing GSOP described and must mention the applicable regulatory requirements. Each division will be responsible for adapting

the high-level document for their requirements. The templates (Training log…) must be same for all of them.

- Contracts with Third Parties

Contracts with third parties are a usual process within the pharmaceutical industry, and these relationships are strictly regulated and must follow a standardized and formal process. It is considered useful to describe a GSOP of the standardized formal process for when the company need an alliance partner or a subcontract to third parties to support the development, manufacturing and distribution of the pharmaceutical products, as well as for supporting GxP services and commercial and medical activities.

Although the acceptability of the partners and third parties is verified through a standard global process, it must also be based on the independent nature of the different phases and their different necessities. An initial assessment process, qualification and routine evaluation of the compliance with GxP services, applicable regulatory requirements and QMS within the pharmaceutical company in the contractor are mandatory to be described.

- Computerized System Validation

Computerized Systems used during the whole system life-cycle of a product, such as, the development, manufacturing, distribution, medical and commercial activities and the electronic data that is generated are subject to specific regulatory requirements. Considering that the same Computer System manages the QMS of a pharmaceutical company throughout the process, the System Validation process must be standardized by a described GSOP, and no necessity found to scaling the document in specific SOPs.

- Deviations Management

The Deviations are common successes during the entire pharmaceutical product development, and they are considered issues that are not in compliance with the regulatory requirements or the GxP guidelines. A GSOP document must be described to define the formal process that must be followed in case of a deviation. The document must consider the details of the total GxP guidelines. No necessity found to scale the GSOP governing document.

- Management and Archiving of documentation

In a pharma company that the QMS is done with a Computer System, the management and archiving of a documentation is automatically done with the System. It must be a transversal process thorough the total pharmaceutical product development and must be clearly defined in a GSOP. Not necessity of scaling this GSOP in specific SOPs, if the GSOP describes all the management aspects.

- Quality Risk Management

Risk is an integral and unavoidable component within a pharmaceutical company's management, so managing the risk in a proactive and effective manner at all the levels of the organization is a regulatory requirement. Risk Management must be considered the cornerstone for an effective Integrated QMS in order to improve processes, procedures and organization in a well-documented, structured and actionable way through all the development process. A GSOP must describe a Global Quality Risk Management. Not found the necessity on scaling the described GSOP in more specific procedures for the different phases.

- Continuous Improvement

  Quality management System must be assessed through a structured Continuous Improvement process ensuring that all the activities and processes directly or indirectly involved in product life-cycle are continually monitored and reviewed to ensure regulatory compliance. Continuous improvement process is considered a transversal process with application thorough the entire pharmaceutical product development so a GSOP must be described. Not found the necessity of scaling the governing document in more specific procedures.

- Data Integrity

  The wrong use, storage and handling of data during the pharmaceutical development can affect the products' quality, safety and efficacy claims. Therefore, data integrity assurance must be implemented at all levels and phases of the company, setting the appropriate standards to achieve this purpose through a well described GSOP. No necessity found to scaling the document.

- Internal Auditing System

  The self-audit program is a critical component of a QMS in a pharmaceutical company. Internal auditing to ensure the GxP compliance must be achieved annually, or according to current regulations. Audit findings and resultant actions will be documented and tracked to completion by a described standardized GSOP document. Internal auditing must be as a key factor for the Continuous Quality Improvement mindset within the company. A specific SOP must be defined for the different phases to define roles, responsibilities, processes and reporting requirements depending on the applicable regulatory requirements.

3.4. QUALITY CULTURE

Each employee is responsible to perform all the assigned duties in accordance with the quality documentation described as applicable to their job responsibilities. Generating a strong quality culture within the company is a strategic key to maintain and ensure the compliance of the implemented QMS.

4. DISCUSSION

Up to date, the pharmaceutical companies have made a huge progress toward implementing and certifying Quality Management Systems. As innovative option, ICH Q10 has been recently defined. This guideline emphasizes the responsibility of senior management for the implementation of the Quality Management system including its development, implementation, control, and improvement within a pharmaceutical company. This idea is in contrast with the old-fashioned idea on the quality unit's responsibility for the QMS. The quality units related to specific phases of the pharmaceutical product development has important responsibilities. Perhaps these responsibilities are becoming more challenging. ICH Q10 assigns the primary responsibility for the QMS to senior management and it clearly states *"Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives"* [9]. This phrase clearly states that the organizational management of the company should be arranged perhaps the QMS.

In general terms, the arrangement of an IQMS is labour-consuming innovative project but able to make improvement of performance for a Quality System and it provides better mobility and adaptability to change conditions and increases the effectiveness of the standard structure of the Documentation Management System [15].

Additionally, it must be taken into consideration that the idea developed thorough this report is related to a simple and specific pharmaceutical organization. So thus, the idea is considered limited in some aspects. The structure defined in this report is a structure of a pharma company that only have one site in one country (not specified) from European Union and can be able to produce just medicinal products. This schema is far from the reality of many healthcare industries. Due to the globalization of the companies, there are pharmaceutical companies which have sites all over the world. In this case, it could be impossible to extrapolate the mentioned idea, as within these type of companies they should not only take into consideration all the GxP guidelines and regulations within EU, but also consider that it should be applicable outside of EU and take the QMS limits abroad to the other continents. Moreover, medical devices for example have different regulations compared to medicinal drug products.

Furthermore, one of the aspects that have not been mentioned but it is considered essential in QMS of a pharma companies is the language in which the documents are described. Documents directly related to employees who are working within the company, as for example manufacturing of the drug product, must be described in the mother tongue language (from where the document is applicable). Moreover, as it is described in GCP guidelines, specific SOPs and Procedures related to clinical development must be described in English for the understanding of possible auditing. So thus, the differences in the language requirements could be an obstacle, although the translation of the documents can partly fix the problematic. More resources should be needed.

Additionally, a well-defined QMS within a pharma company including the GxP guidelines, it can be considered strength point of the pharmaceutical industry as it demonstrated the figure of a well-organized corporate. Furthermore, the management of an Integrated QMS seems to be easier compared to having different QMS implemented within the same company. Having defined a strictly structured Documentation System and Organizational Quality chart are the strength points of a QMS, and both are reflected in this report. The information provided related to the documentation management by specific examples and procedures is considered an important aspect of the report as the ideas are developed not only in a theoretical but also in a practical way.

The described QMS within this report could be useful for those pharma companies which do not already have a QMS implemented overall the company. The diffusion of different QMS into a general one is a labour consuming job that can be simplified with the understanding of the ideas developed in the report.

As a final conclusion, there is not any general QMS that could be valid for all the healthcare industries. QMS of a pharma company depends on the structure, profile and characteristics of the company. However, the idea developed in this report is considered a description of a specific QMS for a specific pharmaceutical company, that it could be used as a partition point for different organizations and pharmaceutical profiles. The described ideas comply with the EU regulations so it can be used as a legal reference for the development of different QMS within EU. However, further investigations must be done for the implementation of a overall QMS in a real pharma company.

ACKNOWLEDGMENTS

Undertaking the EMOTION Masters Program has been a life-changing experience for me and it would not have been possible without the trust, support and guidance I have received from many people. Furthermore, the opportunity to develop the program in Italy and Belgium has enriching, both academically and personally.

First, I would like to express my most profound appreciation to all the coordinators, teachers and students from the master's program. Thanks to all their invaluable support and assistance during the last two years, I have successfully fulfilled all the academic requirements. I am grateful for the fantastic people I met in this Master. Thanks to them I have had a huge personal growth and learned a lot. I especially want to thank Ale, Vane, Caro, Giuliana and Ivana, my forever EMOTION confidents and friends for life.

Words cannot express my gratitude to Elisabetta di Martino who has put all her trust in me. Thanks to her continuous support and encouragement during the months I have been under her expert supervision, I have not only had the opportunity to grow as a worker but also as a person. She has introduced me to the pharmaceutical industry and guided me to develop a promising job career in this complex industry. Without her guidance, this thesis would not have been achievable as the project of this thesis has been elaborated thanks to the ideas I could obtain from her long experience in the quality field. I would also like to show my gratitude to Ilaria and Daniela, from the QA team where I developed my internship, as they have supported me always I needed it. I would never forget this six-months experience and would not be same without their presence. Many thanks also to my academic supervisor Prof. Patricia Lienard from UNAMUR University, who provide me expert guidance and feedback throughout this project.

I would also like to thank all the people I have met during this two-year experience in Novara, Namur and Milan. I have met unique and fantastic people who I am sure will remain by my side all my life. Thank you for supporting me in the best and worst moments through this life cycle, giving me laugh-out-loud funny moments and not so funny ones but from which we have learned and matured together. Special gratifications for Maite, who has supported me from the first to the last day of my long academic career.

Lastly, I would like to express my immense gratitude to my family. Special mention to my mother and brother, Idoia and Jon, for their continuous support throughout my life. I would never have achieved my solid academic background without them. Thank you for providing such a support that I could feel it even being thousands of kilometres away from home. I would like also to thank Garikoitz, Jose Angel, Arantza and Aintzane, as without their trust and encouragement, I would not be able to be where I am now. Special gratitude also to my father, as I can feel his enormous support every second of my life. I could not be more proud of the person I have become and it could not be possible without you. Thank you all for being always by my side.

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