Universidade de Aveiro Secção Autónoma de Ciências da Saúde
2014

SANDRA FILIPA SIMÕES FERNANDES VIEIRA

QUALIDADE DO PRODUTO E CONFORMIDADE NA INDÚSTRIA FARMACÊUTICA

PRODUCT QUALITY AND COMPLIANCE IN THE PHARMACEUTICAL INDUSTRY

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Projeto apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Dra Teresa Murta, Directora Técnica e Directora do Departamento de Qualidade do Produto e Compliance da Bluepharma - Indústria Farmacêutica, S.A. e do Professor Doutor Bruno Miguel Alves Fernandes do Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

Aos meus pais pelo seu amor incondicional e pelos valores que me transmitiram e que fazem de mim o que sou.

O júri

Presidente: Professor Doutor Nelson Fernando Pacheco da Rocha, Professor Catedrático, Universidade de Aveiro

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Vogal - Orientador: Doutor Bruno Miguel Alves Fernandes do Gago, Professor Auxiliar Convidado, Universidade de Aveiro

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palavras-chave

Medicamento, Indústria Farmacêutica, GMP, ICH, Guidelines, Autoridades, CTD, ANDA, Qualidade, Conformidade, PQR, Documentação Analítica, Libertação de lote, Auditoria, Inspecção, Formação

Resumo

A presente tese tem como principal objectivo realçar a importância do trabalho desenvolvido num departamento de Qualidade de Producto & Compliance numa Indústria Farmacêutica no bom desempenho das actividades da empresa e no cumprimento dos seus objetivos e missão. Apesar da actividade deste departamento ser muito vasta o objectivo deste trabalho será cumprido através da descrição de algumas das tarefas executadas no âmbito deste. As tarefas descritas são, mais concretamente, as desempenhadas ao longo da minha experiência profissional na Bluepharma - Indústria Farmacêutica, S.A., iniciada em Junho de 2012 no departamento de Garantia da Qualidade, tendo continuidade até aos dias de hoje no agora designado departamento de Qualidade do Produto e Compliance.

Esta dissertação está estruturada em 4 partes. No primeiro capítulo é feita uma introdução ao presente trabalho, com a sua contextualização e objetivos, seguindo-se uma breve abordagem do estado-da-arte da indústria farmacêutica, nomeadamente do contexto de mercado, do ambiente regulamentar e dos requisitos de qualidade. Neste capítulo é ainda apresentada a empresa e o departamento onde tem vindo a ser desenvolvida a minha atividade profissional. No capítulo seguinte são descritas as tarefas e atividades principais desempenhadas, as atividades complementares e as principais competências adquiridas ao longo desta experiência profissional. No final é apresentada uma discussão e conclusão, incluindo uma análise das atividades desenvolvidas, principais dificuldades sentidas, do papel e relevância das tarefas desenvolvidas no contexto global da empresa bem como das competências adquiridas durante esta experiência profissional.

keywords

Medicinal product, Pharmaceutical Industry, GMP, ICH, Guidelines, Authorities, CTD, ANDA, Quality, Compliance, PQR, Analytical Documentation, Batch release, Audit, Inspection, Training

abstract

This thesis aims to highlight the importance of a Product Quality & Compliance department in a Pharmaceutical Industry, on the good performance of company's activities and the achievement of their goals and mission. Despite the wide activities performed by this Department, the purpose of this work will be completed by describing only some of their reponsibilities. The tasks described are specifically the ones I have been performing throughout my professional experience at Bluepharma - Pharmaceutical Industry, SA, initiated in June 2012 in the Quality Assurance Department until today in the currently named Product Quality & Compliance department.

This thesis is structured into 4 parts. The first chapter is an introduction to this thesis, and includes its context and objectives, followed by a brief overview of the state-of-the art in the pharmaceutical industry, including the market environment, the regulatory environment and quality requirements. A small presentation of the company and the department where were and still are developed my professional activity is also made in this chapter. In the following chapter are described the main tasks performed, the complementary activities and key skills acquired throughout this professional experience. A discussion and conclusion is presented at the end, including an analysis of the reported activities, main difficulties encountered its role and importance in the company performance as well as the skills acquired during this work experience.

Table of Contents

Figures Index

Abbreviations

ANDA	Abbreviated New Drug Application
ASMF	Active Substance Master File
CAPA	Corrective action and Preventive action
CEP	Certificate of Suitability to the Monographs of the European Pharmacopeia
CFR	Code of Federal Regulation
CTD	Common Technical Document
DP	Drug Product
DS	Drug Substance
eCTD	Electronic Common Technical Document
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines and Healthcare
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	Good Distribution Practices
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
GPhV	Good Pharmacovigilance Practice
GxP	Good Practices
ICH	International Conference on Harmonization
ISO	International Standards Organisation
JP	Japanese Pharmacopoeia
JPMA	Japan Pharmaceutical Manufacturers Association
MA	Marketing Authorisation
MAD	Marketing Authorisation Dossier
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
NDA	New Drug Application
Ph.Eur.	European Pharmacopeia
PhRMA	Pharmaceutical Research and Manufacturers of America
PQ&C	Product Quality and Compliance
PQRs	Product Quality Reviews

QP	Qualified Person
R&D	Research and Development
US	United States
USP/NF	United States Pharmacopeia/National Formulaire

1. Introduction

The present thesis elaborated under the scope of the Master's Degree in Pharmaceutical Biomedicine will address the importance of a Product Quality & Compliance department in a Pharmaceutical Industry, on the good performance of company's activities and the achievement of their goals and mission by reflecting my working experience over the past two years up to the present at the Product Quality and Compliance Department (PQ&C), previously Quality Assurance Department, of Bluepharma Indústria - Farmacêutica, S.A., as well as to emphasize the learning outcomes acquired during this period.

In order to better contextualize the theme proposed, this thesis will cover the current state of the art in the pharmaceutical industry focusing on pharmaceutical market, regulatory environment and quality demands. It will also be presented a brief vision of the institution as well as the positioning of the PQ&C department in the company, its interaction with other departments and main activities.

Special emphasis will be given to the tasks that I have been performing in the framework of quality and the compliance and its relevance for the activities and mission of the company.

Finally, a brief discussion will be presented concerning the different activities described in more detail within the Product Quality and Compliance, the main obstacles encountered in its execution, their contribution for the success of the company as well as the skills acquired during this work experiences. In the end a final keynote under the Conclusions section, highlight the most relevant messages and experiences.

1.1. Pharmaceutical Industry State-of-the-art

This section intends to provide a brief overview of the current state of the art in pharmaceutical industry focusing on the pharmaceutical market, regulatory environment and Quality current demands in order to contextualize better the role of the assessment of product quality and compliance. Greater importance will be given to the European and North American context as these are the two main markets of the activities described in the development of this thesis.

1.1.1. Pharmaceutical Market overview

Article 1 of Directive 2001/83/EC as amended defines a 'medicinal product' as “Any substance or combination of substances presented as having properties for treating or preventing disease in human beings” and/or “Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.” (1)

Therefore, medicinal products have been over the years crucial in the improvement of health and/or quality of life and contributing largely to the world population life extension expectancy. According to the European Federation of Pharmaceutical Industries and Associations (EFPIA) report of 2012 European, citizens can expect to live up to 30 years longer than they did a century ago. (2)

The pharmaceutical industry is responsible for the investigation, development, production and marketing of medicinal products, thus it represents an important sector in global economy.

The total level of pharmaceutical revenue worldwide had reached is the latest years nearly one trillion United States (US) dollars being North America the responsible for the largest portion (more than 40%), mostly due to the leading role of the US pharmaceutical industry, followed by European and Japanese. (2) (3) Branded, patented medicines represent by far the largest share of pharmaceutical revenues. In 2012, Oncologics was the leading therapeutic class based on revenue (almost 62 billion US dollars of revenue globally) followed by other major therapy classes like pain drugs, antihypertensives and antidiabetics. (3)

More than any other industry, the pharmaceutical sector is highly dependent on its research and development. Pharmaceutical companies invest 20 % more of their revenues in research and development (R&D) measures. (3)

All new medicines introduced into the market are the result of lengthy, costly and risky R&D conducted by pharmaceutical companies: it can takes 12-13 years from the first synthesis of the new active substance until the moment on which a medicinal product reaches the market; According to Mestre-Ferrandiz et al in 2012, cited in the European Federation of Pharmaceutical Industries and Associations' (EFPIA) report of 2013, the cost of researching and developing a new chemical or biological entity was estimated at € 1,172 million ($ 1,506 million dollars in 2011); finally, only one to two of every 10,000 substances synthesized in laboratories will successfully pass all stages of development required to become a marketable medicine. (4)

As in other industries, in the pharmaceutical industry, the patent protects the extensive investment in research and clinical testing required before placing it on the market. This patent protection for pharmaceutical products is especially important compared with other industries once the actual manufacturing process is often easy to replicate and can be copied with a small fraction of the huge investment required for the research and clinical testing. Although, the time needed to obtain regulatory approval of these products (i.e. authorisation to put these products on the market) is in general very extensive and, therefore, the patent exclusivity period for pharmaceutical manufacturers is far shorter than in the case of other patent dependent industries and revenue losses due to patent expiry are often very significant. Thus, the development of new drugs is of vital importance for the pharmaceutical industry. (3) (5)

In addition to the patents protection, to compensate for the inability to market inventions due to safety and efficacy regulation, both in Europe and in the US, it was addressed in legislation the possibility of a patent applicant apply for extensions of patent term. A supplementary protection certificate is a unique intellectual property (IP) right that extends the duration of the exclusive right. It enters into force after expiry of a patent upon which it is based. It comes into force only after the corresponding general patent expires. It normally has a maximum lifetime of 5 years and the total combined duration of market exclusivity of a general patent and supplementary protection certificate cannot normally exceed 15 years, barring exceptions (Article 36 of Regulation (EC) No 1901/2006)[1]. Although in the European Union (EU) all countries are required to provide supplementary protection certificates, no unified cross-recognition exist and therefore applications must be filed and approved on a country-by-country basis. (6)

[1] **REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004** that aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorized for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations.

In Europe, besides the protection of innovation through patents and supplementary protection certificates, there are also specific “health laws” that govern generic medicinal products development and marketing.

A generic medicine is a medicine that is developed to have similar Pharmacokinetic / Pharmacodynamic parameters as the reference medicine that has already been authorised, it contains the same active substance(s), is used at the same dose(s) to treat the same disease(s), however, the name of the medicine, its appearance (such as colour or shape) and its packaging can be different from those of the reference medicine. (7)

Generics are usually produced by a manufacturer, who is not the inventor of the original product, and are marketed when intellectual property protection rights are expired. The market share of generics is significantly higher in new EU Member States with historically low levels of intellectual property protection while most of the new substances introduced in the market have their origin in the US. In 2009, the generic medicines market had an estimated value of €57 billion in the top global markets. In Europe, European Generic Medicines Association estimated that generics medicines market size was of €31 billion in 2009. (4) (8)

As for all medicines, generic medicines can only be marketed after having a marketing authorisation from a regulatory authority, such as the European Medicines Agency (EMA), granted after a scientific evaluation of the medicine’s efficacy, safety and quality. Consequently, the companies must submit quality, efficacy and safety data, including clinical data that proves the bioavailability and bioequivalence of the generic medicine vs. originator reference products to the regulatory authorities; all data provided to the competent authorities is assessed with the same accuracy than the innovator reference medicinal product already approved. Generic medicines are manufactured according to the same quality standards as all other medicines and its safety continues to be monitored after authorisation as well through the Pharmacovigilance system in place. (7)

A company can only develop a generic medicine for marketing once the period of ‘exclusivity’ on the reference medicine has expired. This period of exclusivity is given by law to the company that developed the innovative medicine on which the generic medicine is based and comprises “data exclusivity” (typically 8 years from the date of first authorisation) after which valid applications for generic products can be submitted, and “market protection” after which generic products authorized in this way can be placed on the market (typically 10 years from the date of first authorisation). (7) (9)

Contrary to what is the general perception that innovation is domain of the research-based originator companies, generic medicine companies spend a significant amount of their budgets on innovation. The generic medicine companies also invest on innovation to create new

strategies to overcome patents, for example, by improving formulations, enhancing delivery systems or by developing solutions to improve patient compliance. (7) (8).

On average, 16.6% of total health expenditure in Europe is being spent on pharmaceuticals and other medical nondurables. Therefore the cost of drugs is a very important factor to have in account to maintain the sustainability of health systems. Economic and Financial Crisis in the EU reinforced the need for effective and efficient health care systems, as well as proper management of available resources. Consequently, generic medicines play an important role in health systems since they enable disease treatment at a lower cost, thus increasing the accessibility and availability of essential drugs to patients. (4) (8)

Despite the advantages presented by generic medicines there is still some unfounded mistrust by health care professional and patients, arguing that they may be less safe, effective or that have less quality than the branded medicines

1.1.2. Regulatory environment

In order to protect public health, governments need to approve comprehensive laws and regulations and establish effective national regulatory authorities to ensure that the manufacture, trade, and use of medicines are regulated appropriately and that the public has access to accurate information on medicines. (10)

European Legislation

The European legislation related to medicinal products for human use comprises a set of legal instruments, that include legally bind acts (regulations, directives and decisions) and soft laws (Resolutions, Communications, Guidelines and notice to applicants).

European pharmaceutical legislation is nowadays compiled in a set of publications globally named Eudralex that include 10 volumes. The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union".

- Volume 1 - EU pharmaceutical legislation for medicinal products for human use
- Volume 5 - EU pharmaceutical legislation for medicinal products for veterinary use

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
- Volume 3 - Scientific guidelines for medicinal products for human use
- Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use
- Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use
- Volume 7 - Scientific guidelines for medicinal products for veterinary use
- Volume 8 - Maximum residue limits
- Volume 9 - Guidelines for pharmacovigilance for medicinal products for human and veterinary use
- Volume 10 - Guidelines for clinical trial

Medicinal products for paediatric use, orphan, herbal medicinal products and advanced therapies are governed by specific rules. (11)

Globalization trend

Laws and regulations evolve within countries over time, but in recent years, the trend has been toward the globalization of pharmaceutical issues, which affects national legislation. This globalization, exemplified through changes in international trade, patent protection, and pricing, has resulted in a number of initiatives that must be considered by countries developing pharmaceutical regulations. International Conference on Harmonization (ICH) and Pharmacopoeias are some examples of these initiatives. (10)

ICH

Some of the biggest advances on regulations, established in order to assure the safeguarding of public health, were triggered by adverse incidents. Among these incidents, it stands out the tragedy with the thalidomide. In the late 1950s, thalidomide was approved in Europe and was prescribed to control sleep and nausea throughout pregnancy, but the American Authority (FDA) did not approve it in the US at the same time. Before getting approval in the US, it was found that taking this drug during pregnancy caused severe deformities in the foetus. (12) This tragic event emphasized the lack of proper policies, legislations and guidelines to ensure the safety, efficacy of a new drug and the absence of common criteria for the registration and marketing of pharmaceuticals, resultant from the different set of guidelines and laws used in

each country. Around the same time, the pharmaceutical industry started its internationalization process, seeking new global markets, becoming more evident these differences. The existing divergences in technical requirements from country to country, also lead to the duplication of test procedures, turning this global marketing process slow and expensive. (13)

To optimize this process, harmonization of technical requirements was necessary. In 1990 it was launched International Conference on Harmonization (ICH) by drug regulatory authorities and pharmaceutical industrial members of Europe, Japan and US with the objective of providing guidelines to ensure the registration and marketing of safe, effective and high quality medicines. Representatives from six parties form ICH: Ministry of Health, Labour and Welfare (MHLW), and the Japan Pharmaceutical Manufacturers Association (JPMA) representing Japan, European Union (EU) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) representing Europe, and Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America (PhRMA) representing the USA. Additional members include observers from the World Health Organization, European Free Trade Association and Canada. (14)

The main purpose of ICH is to promote international harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration. Consequently this process avoid duplication of clinical trials in humans, minimize the use of animal testing without compromising safety and effectiveness, streamline the regulatory assessment process for new drug applications and reduce the development times and resources for drug development. (15) This way, it turns possible to develop safe, effective, and high quality medicines, at a lower cost and with a minimum of delay in make it available to patients. The Harmonization is achieve through the development of ICH Tripartite Guidelines. ICH Guidelines are divided into four categories:

- Quality Guidelines: include pivotal milestones such as the conduct of stability studies, definition of relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.
- Safety Guidelines: to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity.
- Efficacy Guidelines: embraces the design, conduct, safety and reporting of clinical trials (Good Clinical Practices). It also covers novel types of medicines derived from biotechnological processes and pharmacogenetics/genomics techniques.
- Multidisciplinary Guidelines: other topics which do not fit uniquely into one of the previous topics like the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information. (16)

One of the most important achievements of the ICH was the creation of the **Common Technical Document (CTD)**, through an Industry proposal in 1996. The CTD, and since 2006 the electronic CTD (eCTD) had revolutionised the submission process, by easing the process both for pharmaceutical companies and for regulatory authorities, by allowing for example the submission of a single technical dossier in the three ICH regions instead of a multiple complex submissions, therefore saving time and resources. (17)

The Common Technical Document is organized into five modules containing non-clinical, clinical and quality information (Figure 1):

1. Administrative and prescribing information;
2. Overview and summary of modules 3 to 5;
3. Quality (pharmaceutical documentation);
4. Preclinical (Pharmacology/Toxicology);
5. Clinical – efficacy (Clinical Trials).

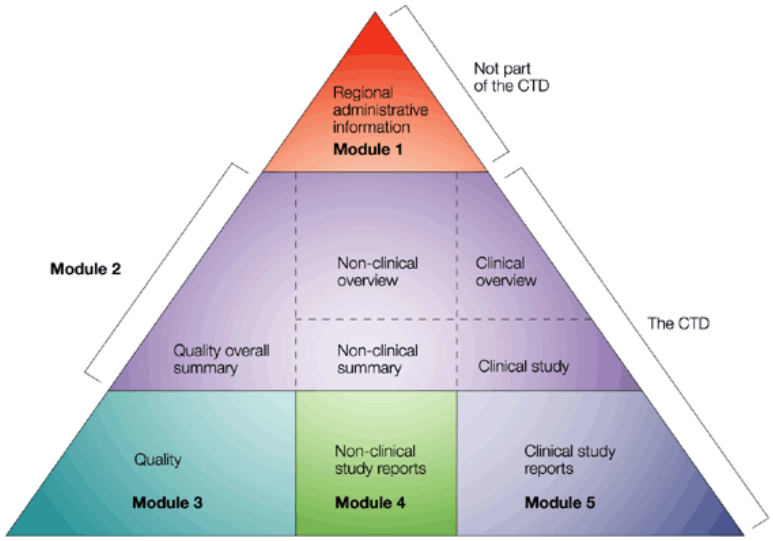


Figure 1- Diagrammatic Representation of the Organization of the CTD (17)

Module 1 contains the regional and administrative information and it is specific for each region. The other four modules are common to the three regions and are in a harmonised format. (17)

The Quality section of the Common Technical Document (Module 3) provides a harmonised structure and format for presenting Chemistry, Manufacturing and Controls information in a registration dossier. The table of contents includes sections on Drug Substance (DS) and Drug

Product (DP). There are also sections for regional specific information as well as some appendices. (17)

The content of the dossier differ with the medicine product aimed (complete, generic medicinal products and similar biological products; well-established medicinal bibliographic; new fixed combination products). (18)

A CTD for a generic product contains Modules 1, 2, 3 and 5. Module 4 does not need to be included in a CTD for a generic drug, since all relevant non-clinical information for the active substance of the drug product is already documented. There are also some significant differences in a generic CTD content, towards a reference medicine CTD, concerning the European context: Module 1 of a CTD for a generic Marketing Authorisation Application, has to include a summary of the grounds and evidence, used for demonstrating that the medicinal product for which an application is submitted is a generic of a reference therapeutic product (qualitative and quantitative composition in active substance, pharmaceutical form, bioequivalence information and its safety and efficacy profile in comparison to the reference medicinal product); Module 2 of a CTD for a generic drug must include the Quality Overall Summary but differently from a normal CTD the summaries of the non-clinical and clinical studies are only mandatory if new studies have been conducted for the generic drug; Module 3 of a generic drug has to be filled and presented according to what is described in ICH M4Q and WHO's "Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP) quality part"; Module 5 is included once most generic drug products market applications are supported by one or more pivotal comparative bioavailability studies, performed in order to assess their bioequivalence to the original drug product, however, since no other clinical studies are required for generic drug products, this module is much shorter than the one for an original drug product. (19)

For the purpose of this thesis, some sections of Module 3 will be further detailed.

In the US, an **Abbreviated New Drug Application (ANDA)** is submitted to the FDA when seeking review and approval for a generic drug product. The ANDA is submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs and contains essential data for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug for the American market.

Pharmacopoeias

Pharmacopoeias are documents that outline technical information, manufacturing and testing procedures, and standards for active pharmaceutical substances and products.

A pharmacopoeia is usually recognized as part of a country's national pharmaceutical laws, therefore, the standards and procedures are legally enforceable. Because of the extensive resources required to produce and maintain these complex documents, most countries do not have national pharmacopoeias and rely on one or more internationally recognized pharmacopoeias, such as those from the United States (USP/NF), the European Pharmacopeia (Ph.Eur.) from the European Union, Japan, or World Health Organization. The organizations that publish pharmacopoeias, pressured by the need to facilitate international trade, are actively working to harmonize their requirements.

Marketing authorisation procedures in the European Union

Directive 2001/83 /EC, also known as the Consolidated Directive, govern the regulation of medicinal products in the EU. This legislation brings up in one document legislation and regulatory issues concerning medicine products including rules concerning specific categories of medicines, manufacture, importation and distribution, labelling and advertising, the classification of medicinal products, and pharmacovigilance. This Directive has been implemented into the national laws of each EU member state and adopted by other members of the European Economic Area (EEA): Norway, Iceland, and Liechtenstein (the Swiss system also mirrors EU regulation). In all its complexity, this directive states one fundamental premise: "No medicinal product may be placed on the market in the EU unless the relevant competent authority grants a marketing authorisation." (18)

The "Notice to applicants: VOLUME 2A - Procedures for marketing authorisation", prepared by European Commission in consultation with competent authorities of the Member States and EMA, in order to facilitate the interpretation and application of the European Legislation, also states: "A medicinal product may only be placed on the market in the European Economic Area (EEA) when a marketing authorisation has been issued by the competent authority of a Member State (or EEA country) for its own territory (national authorisation) or when an authorisation has been granted in accordance with Regulation (EC) No 726/2004 for the entire Community (a Community authorisation). The marketing authorisation holder must be established within the EEA." (20)

In order to obtain a marketing authorisation (MA) the applicants should submit a full dossier to competent authority that details, among other things, product's common or scientific name, invented name, qualitative and quantitative particulars, proposed therapeutic indications, contraindications, and adverse reactions, as well as the results of pharmaceutical and

preclinical tests and clinical trials. This dossier must be prepared in the EU CTD format, previously described, according to the medicine product aimed.

Marketing authorisations are valid for an initial period of five years, after which they may be renewed. Once approved, the holder is under an obligation to continually update the authorisation in order to ensure compliance with scientific progress and new regulatory requirements and especially to assure a constant evaluation of the benefits and risks of the product. (21)

There are four different procedures to obtain a Marketing Authorisation (MA):

- Centralised Procedure: this procedure allows the introduction of the medicinal product in all the countries in EEA, (EU Member States and also Iceland, Liechtenstein Norway). The application is made directly to the EMA.. (21) (20)
- Mutual Recognition Procedure: this procedure applies when a medicinal product has already a MA in one Reference Member State and the applicant wants to obtain a MA in another member state or, at the time of submission, the same medicinal product is being assessed by more than one Member States. (21) (20)
- Decentralised Procedure: this procedure is an alternative to mutual recognition procedure used to obtain marketing authorisations in several Member States, when the medicinal product in question has not received previously a marketing authorisation in any MS, at the time of application. (21) (18)
- National Procedure: In this procedure, the regulatory authority of each member state country is responsible for granting marketing authorisation for its own country. (21) (18)

Regulatory Bodies

The life cycle of any drug involves several phases. The initial phases of basic research, disease discovery and drug discovery are not regulated but the following Preclinical Development, Clinical Trials (I, II and III), Manufacturing (including Drug Substances) and Market Launch, are (2).

Several Regulatory Agencies exist in most territories to oversee the development, approval, and marketing of drugs as well as their behaviour during the lifecycle.

European Medicines Agency (EMA)

The European Medicines Agency (EMA) is the European Union body responsible for the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. EMA cooperates with the existent Member States in

the evaluation, supervision and pharmacovigilance of medicinal products. The main activities of EMA are related with marketing authorisations; safety monitoring of medicines and inspections. (22)

European Directorate for the Quality of Medicines and Healthcare (EDQM)

EDQM is another important EU Regulatory body of the European Medicines Regulatory System. It co-ordinates several activities in 47 countries including the responsibility for the European Pharmacopoeia, co-ordination of other medicines control activities via national agencies, inspectorates etc., and the emission of the Certificates of Suitability of Drug substances after inspection to manufacturers facilities. (23)

National Competent Authorities

National Competent Authorities are Medicines Agencies responsible for regulate/ supervise the medicinal products sector at a National Level. They have also responsibilities on Marketing Authorisations (for each Member State in the Mutual Recognition, Decentralized or National Procedure), Safety monitoring (monitor and assurance of national medicines vigilance systems) and Inspections (assurance of compliance with good practices (GXP)). (21)

INFARMED is the Portuguese National Authority of Medicines and Health Products, IP, is a Government agency accountable to the Health Ministry created to monitor, assess and regulate all activities relating to human medicines and health products for the protection of Public Health.

Food and Drug Administration (FDA)

FDA is the United States of America agency responsible for “protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation (5).” Concerning medicines FDA has in the US similar responsibilities to EMA on marketing authorisations, safety monitoring of medicines and inspections. The FDA inspections cover also several areas: Current GMP Inspections, Clinical Investigator Inspections, GLP Inspections and Pharmacovigilance Inspections. (24)

Pharmaceutical Inspection Convention” and the “Pharmaceutical Inspection Co-operation Scheme” (PIC/S)

In order to provide a joint active and constructive co-operation in the field of GMP between countries and pharmaceutical inspection authorities, was also created the “Pharmaceutical

Inspection Convention" and the "Pharmaceutical Inspection Co-operation Scheme" (jointly referred to as PIC/S). PIC/S' mission is "to lead the international development, implementation and maintenance of harmonised GMP standards and quality systems of inspectorates in the field of medicinal products". For that they develop and promote harmonised GMP standards and guidance documents, provide training to competent authorities, in particular inspectors, assess (and reassess) inspectorates and encourages the co-operation between competent authorities and international organizations. (25)

From the several activities performed by the regulatory authorities, stand out three main focus:

- Product development – pre-authorisation phase

The regulatory authorities will grant a MA after evaluating all the data provided in the CTD to demonstrate the efficacy, safety and quality of the product and if all that information is satisfactory. The approved MA is valid for 5 years and should be renewed at the end of that period. After having an approved MA, the product shall be placed on the market within a period of three years ("sunset clause"). (26)

- Product manufacture

The manufacturing or importation of medicinal products, including investigational medicinal products, is subject to a manufacturing or import authorisation. The holder of such authorisation is obliged to comply with the principles and guidelines of Good Manufacturing Practice (GMPs) for medicinal or experimental products and to use as starting materials only drug substances (active pharmaceutical ingredients), which have been manufactured in accordance with GMP Part II. (Title IV of Directive 2001/83/EC); Article 13 of Directive 2001/20/EC, Title IV of Directive 2001/82/EC). GMP´s are a set of norms and procedures of legal framework that govern the pharmaceutical industry activity. The GMP include the basic requirements for medicinal products (Part I), basic requirements for active substances used as starting materials (Part II), GMP related documents (Part III) and Annexes. GMP aim to ensure that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation (MA) or product specification. GMP is a part of quality assurance that concerns both production and quality control; it defines general measures to ensure that processes necessary for production and testing are clearly defined, validated, reviewed and documented, and that the personnel, premises and materials are suitable for the production of the intended medicinal products. GMP also covers distribution, contract manufacturing and testing, and responses to product defects and complaints. All medicinal products manufacturers for human use have the obligation to possess a GMP Certificate issued by EU National CA after verification and inspection of the activities and procedures

implemented in the pharmaceutical facilities/sites. Manufacturing sites must follow the principles and guidelines of the GMP assuring that the production of medicinal products is performed and controlled according to quality standards. In order to verify the compliance with GMP principles and relevant regulatory requirements, National CA perform regular inspections to the sites. (1) (27)

Additionally, since the wholesale distribution of medicinal products is also an important activity in the integrated supply chain management and the quality and the integrity of medicinal products can be affected by a lack of adequate control, the European Commission has also published guidelines on Good Distribution Practice (GDP) of medicinal products for human use. (28)

- Pharmacovigilance

According to World Health Organisation, "Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem". (29) When is granted a MA to a medicinal product, it does not mean that it does not have any safety issue. It means that, based on the current scientific knowledge, the benefits outweigh identified risks. At that time, the information concerning the safety and efficacy information of the medicinal product is limited, since the information is based on a reduced number of patients that were studied only under the controlled conditions of randomised clinical trials. There is no long-term treatment data available, the inclusion criteria are narrow, higher risk subgroups are not included in clinical trials as well as patients with concomitant illnesses that require use of other medicinal products. These factors determine the need for continuing to analyse and assess relevant safety and effectiveness information throughout the medicinal product's lifecycle (21) (30). Regulatory authorities have implemented systems for a systematic collection and assessment of information about adverse drug reactions, over the product's lifetime. These systems allow identifying risks that did not emerge during the pre-marketing phase and that only could be identified in real life conditions. (30)

1.1.3. Quality on Pharmaceutical Development and Manufacturing

As it was referred before medicinal products must be developed/produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products detailed on Volume 4 of Eudralex. This Volume comprises an introduction, three parts

and is supplemented by a series of annexes. The introduction includes the Directives 2003/94/EC and 91/412/EC were are laid down the principles of GMP, Part I covers GMP principles for the manufacture of medicinal products, part II covers GMP for active substances used as starting materials, part III contains GMP related documents, which clarify regulatory expectations and Annexes include guidance on several issues like Sampling of Starting and Packaging Materials (Annex 8), Computerised Systems (Annex 11), Manufacture of Investigational Medicinal Products (Annex 13), Qualification and validation Annex 15, Certification by a Qualified person and Batch Release (Annex 16), Reference and Retention Samples (Annex 19), among others.

Part III is intended to host a collection of GMP related documents, which are not detailed guidelines on the principles of GMP laid down in Directives 2003/94/EC and 91/412/EC. (28) Among the documents included in Part III are two of the ICH guidelines that have arisen in the Quality area:

- ICH Q9 - Quality Risk Management
- ICH Q10 - Pharmaceutical Quality Systems

However, other quality guidelines should be taken into account depending on the type of product and on the stage of development or phase of manufacturing:

- Q1A - Q1F Stability
- Q2 Analytical Validation
- Q3A - Q3D Impurities
- Q4 - Q4B Pharmacopoeias
- Q5A - Q5E Quality of Biotechnological Products
- Q6A- Q6B Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development
- Q11 Development and Manufacture of Drug Substances
- Q12 Lifecycle Management.

These guidelines are a harmonised global quality standards and interpretation based on good science and risk management principles. These guidelines have been developed by ICH Expert Working Group and have been subject to consultation by regulatory entities including FDA and EMA that, therefore recommend its use. (16)

ICH Q8, Q9 and Q10 guidelines encourages systematic and science and risk-based approaches that are intended to work together to enhance pharmaceutical product quality. These guidelines are applicable over the entire product lifecycle and therefore, will be further

detailed in this section to better understand the demands and trends for quality in pharmaceutical industry.

Other guidelines, focused on essential milestones, such as, the conduct of stability studies (Q1A – Q1F), the definition of relevant thresholds for impurities testing (Q3A – Q3D), the definition of criteria on how to set specifications for drug substances (Q4 – Q4B) or on how to select tests, methods and set specifications for the testing of drug substances and dosage forms (Q6A – Q6B), will be opportunely mentioned throughout this thesis.

ICH Q8

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The ICH Common Technical Document (CTD) includes a section concerning Pharmaceutical Development (3.2.P.2). This section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle of a product.

ICH Q8 guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section and also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. It also includes further clarification of key concepts and tools outlined in the core Guideline, like “quality by design” [2] and “design space”[3], through which can be created a basis for more flexible regulatory approaches. (31)

Is the information and knowledge gained from pharmaceutical development studies and manufacturing experience that provide scientific understanding to support the establishment of the “design space”, specifications, and manufacturing controls.

ICH Q9

The manufacturing and use of a medicinal product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle, such that, the attributes that are important to the quality of the medicinal product

[2] Quality by Design is defined in the ICH Q8 as “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management”.

3 Design space is defined in the ICH Q8 as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters, that have been demonstrated to provide assurance of quality.

remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the medicinal product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight. (32)

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product across the product lifecycle. It is integral to an effective pharmaceutical quality system and facilitates continual improvement of process performance and product quality throughout the product lifecycle. (33)

The two primary principles of quality risk management are:

- the evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- the level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk. (32)

ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. It can be applied not only in the manufacturing environment, but also in connection with pharmaceutical development and preparation of the quality part of marketing authorisation dossiers. The guideline applies also to the regulatory authorities in the fields of pharmaceutical assessment of the quality part of the marketing authorisation dossier, GMP inspections and the handling of suspected quality defects. (32)

Quality risk management should be integrated into existing operations and documented appropriately. In the pharmaceutical area, the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations in several situations:

- industry and regulatory operations: quality management;
- industry operations and activities: development, facilities, equipment and utilities, materials management, production, laboratory control and stability testing, packaging and labelling;
- regulatory operations: inspection and assessment activities. (32)

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. (32)

ICH Q10

ICH Q10 establishes a model for an effective quality management system for pharmaceutical industry throughout the lifecycle of a product, referred to as the Pharmaceutical Quality System, by describing specific quality system elements and management responsibilities. (e.g., Development).

This model is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management". ICH Q10 is intended to be used together with regional GMP requirements but has a wider **application** since the regional GMPs do not explicitly address all stages of the product lifecycle. ICH Q10 can be implemented throughout:

- **Pharmaceutical Development:** drug substance development; formulation development (including container/closure system); manufacture of investigational products; delivery system development (where relevant); manufacturing process development and scale-up; analytical method development.
- **Technology transfer:** new product transfers during development through manufacturing; transfers within or between manufacturing and testing sites for marketed products.
- **Commercial manufacturing:** acquisition and control of materials; provision of facilities, utilities, and equipment; production (including packaging and labelling); quality control and assurance; release; storage; distribution (excluding wholesaler activities).
- **Product discontinuation:** retention of documentation; sample retention; continued product assessment and reporting. (33)

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances and drug products, throughout the product lifecycle and its application should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. (33)

Implementation of the Q10 model should result in achievement of three **main objectives** which complement or enhance regional GMP requirements:

- **Achieve product realization:** by establishing, implementing and maintaining a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.
- **Establish and maintain a state of control:** by developing and using effective monitoring and control systems for process performance and product quality, thereby providing

assurance of continued suitability and capability of processes. Quality risk management can be useful in identifying the monitoring and control systems.

- **Facilitate continual improvement:** by identifying and implementing appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently.

Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approaches to improve product quality. There are four **Pharmaceutical quality system elements required** under regional GMP regulations that are enhanced by ICH Q10 in order to promote the lifecycle approach to product quality. These four elements are:

- **Process performance and product quality monitoring system:** by establishing parameters and attributes (e.g. related to drug substance and drug product materials and components, facilities and equipment operating conditions, in-process controls, finished product specifications, and the associated methods), a frequency of monitoring and control and using the appropriate tools is easier to identify sources of variation that affect process performance and product quality and therefore enables the implementation of continual improvement activities to reduce or control variation;
- **Corrective action and preventive action (CAPA) system**: the pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring.
- **Change management system:** innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA impels changes that should be properly evaluated. This evaluation must be performed by expert teams with representatives from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical) and should be done, not only to ensure that those changes are technically justified, but also to evaluate, after implementation, if the objectives of the change were achieved and if there was no deleterious impact on product quality.
- **Management review of process performance and product quality**: it should be provided assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can comprise a series of reviews at various levels of management and should include a timely and effective communication and escalation process. The management review

system should include: results of regulatory inspections and findings, audits, other assessments and commitments made to regulatory authorities, or periodic quality reviews concerning customer satisfaction (complaints), conclusions of process performance and product quality monitoring, effectiveness of process and product changes (including those arising from corrective action and preventive actions) and any follow-up actions from previous management reviews. Through an effective management review system should be identified appropriate actions, such as improvements to manufacturing processes and products; provision, training and/or realignment of resources; capture and dissemination of knowledge. (33)

Nowadays Pharmaceutical Industries comprise all the four stages of product lifecycle referred to in the ICH Q10, including the development stage. Focusing on the remaining stages, we can conclude that that are several advantages on implementing a robust Pharmaceutical Quality System.

- Improve manufacturing processes thus reducing undesired variability and leading to a more consistent product quality, improved process robustness and more efficiency;
- Decrease the incidence of complaints, recalls and risk of product failure;
- Take actions before a problem and avoid future failure following continuous improvement changes;
- Quality assurance along the throughout life cycle of the drugs providing a continuous improvement of the processes;
- Increase compliance with GMPs;
- Demonstrate an effective quality system to regulatory authorities especially during the inspections;
- Greater confidence in product quality by all stakeholders (manufacturers, regulators and patients);
- Cost reduction by decreasing waste, processes duplication and reworks. (33) (34)

The implementation of Q8, 9 &10 is valuable for all drug products, development approaches and regulatory systems and is essential to achieve ICH Quality Vision. These Guidelines can be used both by Industry and by regulators (e.g., assessors and inspectors are expected to incorporate QRM during regulatory processes).

Good scientific development (Q8) in combination with Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) will improve drug quality and efficiency of pharmaceutical manufacturing.

1.2. Overview of the Company

Bluepharma is a privately owned Portuguese pharmaceutical company based in Coimbra. It was founded in February 2001, by a group of Portuguese professionals connected with the pharmaceutical industry who acquired Bayer's industrial unit, taking advantage not only of the facilities and equipment but also of the human resources with more than 30 years of experience. Throughout the years, Bluepharma has successfully reshaped its business model and went from being a traditional contract manufacturing organization to a company that promotes innovation, registers, licenses and exports its product internationally. Through the companies of the group, Bluepharma offers an integrated approach on the process of drug discovery and drug development, including innovative research of New Chemical Entities (NCE) and New Therapeutic Entities (NTE - based on novel platforms for the delivery of known drugs) as well as the development, manufacturing and commercialization of solid dosage forms. Its main activities thus include:

a) Research & Development

- Dedicated facilities with highly qualified scientists focused on the development of solid dosage forms, including pre-formulation and formulation studies, development of analytical methods, scale up, ICH stability and compilation of CMC.
- Development of novel and versatile oral strip formulations aiming at providing solutions for unmet medical needs.
- Research and development of innovative photosensitizer compounds to be used in Photodynamic Therapy (PDT) or Photodiagnosis (PDx) of cancer or other diseases; One of the lead compounds – LUZ11 – is currently in phase IIa clinical trials in head and neck advanced cancer.
- Research and development of innovative targeted nanoparticles (PEGASEMP) capable of targeting two distinct cell populations in the tumour: the cancer cell and the blood vessels that nurture the tumour. PEGASEMP has entered the formal non-clinical program in 2013.
- Clinical pharmacology unit devoted to perform phase 1 clinical trials in healthy volunteers and selected populations of patients.

b) Industrial activities

- State-of-the-art manufacturing site for solid dosage forms; approved by US, Korean, Taiwan, Iran and EU authorities; capacities for 2.0 Billion units (tablets and capsules).

c) Commercialization of medicines

- Large portfolio of products covering the main therapeutic areas reflecting in export activities worldwide.

This integrated approach has allowed Bluepharma to offer solutions covering every stage of the drug development process and was achieved by investing over 20 million euros since 2001 in extensive improvements, making it the Portuguese pharmaceutical SME that invests more in Research, Development and Innovation activities.

Bluepharma's mission is to offer pharmaceutical products of the highest quality at competitive prices, contributing to the rationalization of expenses in the health sector and simultaneously to the improvement of the life quality of populations. (35) (36) This commitment towards quality and lean management has been paramount to the firm's activities, and is achieved through the implementation of a Quality, Environment, Health and Safety System, supported by ISO Norms 9001, ISO 14001 and OHSAS 18001, by the Good Manufacturing Practices and by other applicable legislation.

Bluepharma is a GMP certificated company by INFARMED, I.P .(Portuguese National Authority of Medicines and Health Products) and is authorised to manufacture different non-sterile products in the following solid dosage forms: capsules, hard shell, tablets, powder and granules. In 2003, became the first pharmaceutical company in Portugal that accumulates combined certifications in quality (ISO 9001/2000), environment (ISO 14001/1999), safety and occupational health (OHSAS 18000). In 2009 obtains official approval by the US Authority (FDA) for the development / manufacture of solid pharmaceutical forms, becoming the first Portuguese pharmaceutical company to export to the American market. Bluepharma has also certification in RDI - Research, Development and Innovation by the Portuguese Authoritie APCER (NP 4457) (36)

Looking ahead, Bluepharma is currently investing in emerging fields such as oncology, nanotechnology and biotechnology, by establishing partnerships with the most prominent local and international research centres and multinational pharmaceutical companies. (36)

The structure of the company and the relationships and relative ranks of its parts is represented in figure 2.

The Product Quality and Compliance is under the coordination of the Vice President Head of Operations/ Head of QASOS and its activity is interrelated with all sectors of the company.

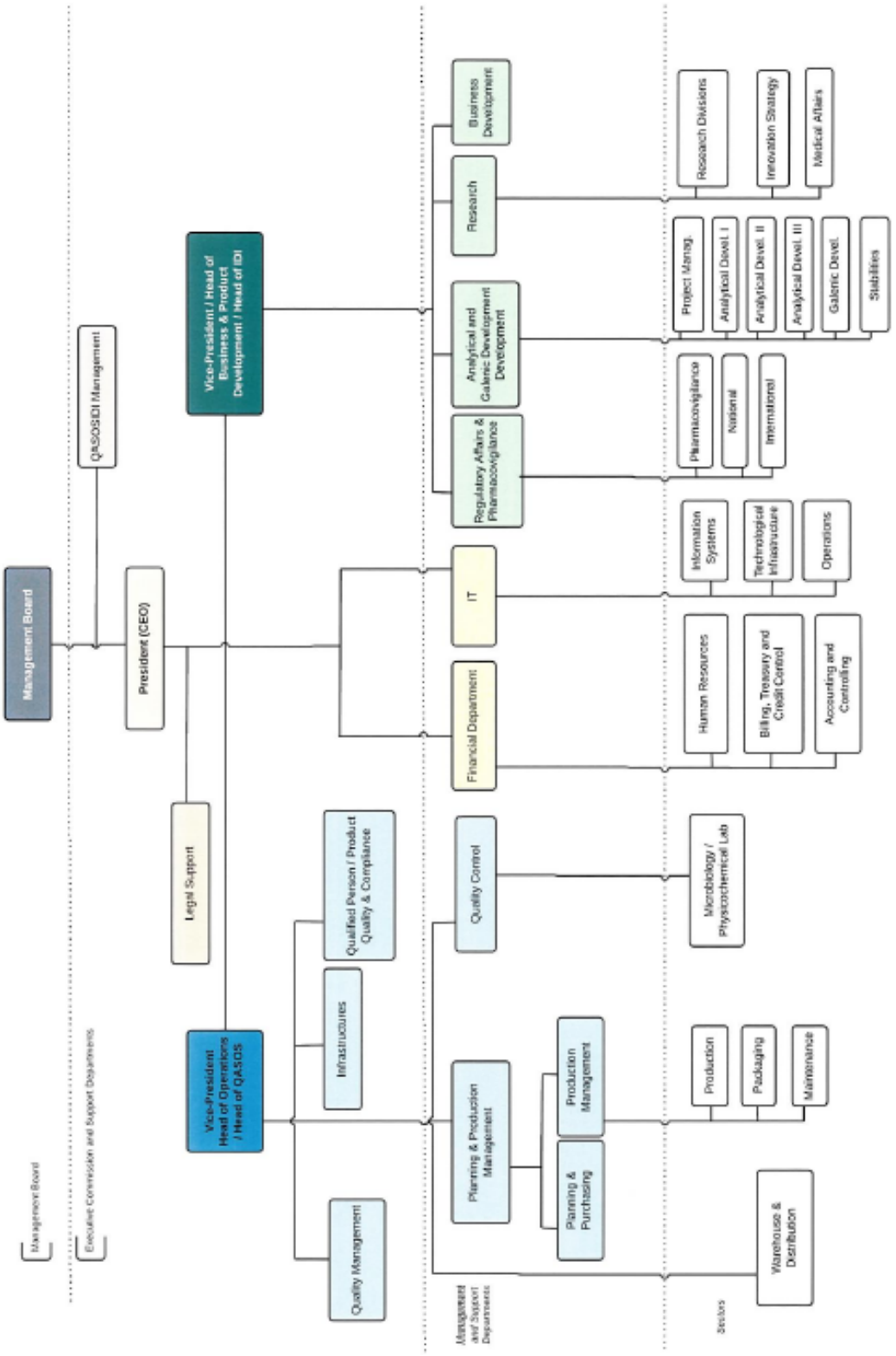


Figure 2
Figure 2 – 2014 Bluepharma's Organisational Chart (35)

1.3. Product Quality and Compliance Department

Until the end of 2012 Quality Assurance Department of Bluepharma was responsible for the Integrated Management including all the quality system in place in the company and also environmental, occupational health and safety systems.

In January 2013 the department Quality Assurance Department has undergone a restructuring process. In practical terms, a new department for product quality and compliance was created, to address all quality matters inherent to the production (from the raw materials until the release of finished product, including equipment and infrastructures product related), product compliance and release of pharmaceutical products (human, veterinary and experimental medicines).

The PQ&C assumed the following main responsibilities and tasks:

- Management of change control and Risk Management related to the materials/ products/ processes/ equipment/ infrastructures/ Information and technology (IT);
- Management of manufacturing and packaging deviation reports, equipment and infrastructures DR, Out-of-specifications, Out-of-trend, Corrective actions, preventive actions and technical complaints;
- Validation, Qualification and Calibrations, of all the GMP relevant equipment, support systems, information technologies systems, infrastructure and related processes;
- Cleaning Validation
- Research & Development support (preparation of all documentation of pilot batches as manufacturing, packaging and process validation) and release to chemical trials;
- SAP Computer System (preparation and revise of SAP inspection plans for raw-materials, packaging materials, bulk product and finished product);
- Product Documentation (Preparation. Verification and Approval of manufacturing, packaging and quality control documentation);
- Assessment of Product Compliance (manufacturing, packaging, quality control and validation documentation);
- Product Quality Reviews (PQRs);
- Technical Supervision of Manufacturing and Packaging processes (in loco and of all the related documents)
- Training;
- Audits and respective CAPA follow up.

The Head of Product Quality & Compliance is also the Qualified Person (QP) of the Company for the experimental medicines, human and veterinary medicines, and therefore the preparation/ review/ approval/ archive of Quality Agreements, the release of the product for the market and for clinical trials, the management of all pharmaceutical acts performed during manufacturing / packaging and analysis are some of other responsibilities that fall within the scope of this department and its staff.

Considering all the responsibilities and tasks described above it is clear that the work undertaken in this department is transversal to the entire company and is fundamental to its operation and to ensure compliance with quality commitment.

Within the scope of this thesis, only some of the tasks listed before will be detailed.

2. On-the-job activities

This chapter intends to describe all the activities, tasks developed, and learning outcomes acquired throughout my professional experience at Bluepharma.

This chapter is organised in three sections:

- Main activities performed
- Additional activities performed
- On-the job additional learning.

2.1. 2.1. Main Activities

My career in Bluepharma began in June 2012 in the Department of Quality Assurance. After a period of integration in the department and specific training, the preparation of Product Quality Reviews (PQRs) was assigned to me as my main task. Lately with the division of the department, I was allocated to the Product Quality and Compliance department and there was a readjustment of my responsibilities and tasks. While retaining the responsibility for conducting PQRs I was also given the responsibility of preparing/ reviewing analytical documentation (specifications, analytical procedures) and perform other related tasks, as the verification of Compliance with the requirements of the Marketing Authorisation Dossier (MAD) or the Abbreviated New Drug Application/ New Drug Application (ANDA / NDA).

2.1.1. Product Quality Reviews

Overall requirements

Product Quality Review is a GMP requirement listed under Chapter 1 of the PIC/S GMP Guide for Medicinal Products, effective since 1 Jan 2006. (37) (38)

In the European Union this guide has been adopted by the *Ad hoc* GMP inspectors Working Group at their first meeting in July 2003. The proposal of Product Quality Review arises from the experience of Member States' inspectorates where quality problems with products on the market leading to recall could have been anticipated if the manufacturer/marketing authorisation holder had operated a system for formally reviewing process consistency and trends. FDA also dictated in

their 21 Code of Federal Regulation (CFR) – Parts 210 & 211 the requirements of reviewing the products annually where clearly states that written records, required by the part, shall be maintained so that data can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Also the ICH in the ICH Q7A GMP Guide for Active Pharmaceutical Ingredients requires manufacturers to conduct annual quality review of the active pharmaceutical ingredients in order to know the consistency on the quality of products manufactured throughout the year. (37)
Essentially, product quality review (PQR) is a natural progression of GMP quality system implementation by manufacturers. This requirement was not new in the pharmaceutical industry before the PIC/S Guide, however the requirement started to be clearly specified after it. (37)

Product Quality Review is therefore a regular periodic quality review of all licensed medicinal products which are conducted with the main objectives of highlight any overall trends (not necessarily visible with other quality systems) and to identify product / process improvements by verifying and identifying:

- the consistency of the existing process(es);
- trends in product data;
- the appropriateness of current specifications for starting materials, intermediates and finished products;
- the compliance of the registered particulars of pharmaceutical products (Marketing Authorisation);
- deficiencies not detected by routine testing, monitoring or performance metrics;
- opportunities for product and process improvements;
- the need of change regulatory submisions. (38)

Product Quality Review should typically be carried out for each product manufactured in the previous year. The review period can be extended beyond a year if duly justified (e.g. low batch numbers associated and low risk associated with the type of medicine). Such extensions shall be for a limited number of months and must be properly justified and described in the internal standard operating procedure concerning PQR´s. Implementation of preceding years' recommendations shall also be reviewed and a risk-assessment approach (Quality Risk Management) must be used along the PQR. The PQR must be performed on a group of products with a particular characteristic. The products included in a group must be sufficiently similar, so that the parameters to be revised are representative of that group (eg. be of the same pharmaceutical form containing the same or

very similar active ingredients and excipients, and manufactured using the same type of equipment).

PIC/S Guide to GMP (Clause 1.4) requires the following parameters (at minimum) to be assessed when conducting PQR:

- Starting materials: a review of starting materials including packaging materials used in the product, especially those from new sources (e.g. batch, manufacturer, supplier, results of analytical tests);
- In-process controls and quality control testing: a review of critical in-process controls and finished product results (e.g. trend in-process test results and Quality Control test results and yield reconciliation from stages);
- Manufactured batches (intermediates, bulk, finished products and campaign batches): a review of all batches that failed to meet established specification(s) and their investigation;
- Deviations and CAPA: a review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;
- Process or testing changes: a review of all changes carried out to the processes, or analytical methods;
- Marketing authorisations: a review of Marketing Authorisation variations submitted/granted/ refused, including those for third country (export only) dossiers;
- Stability program: a review of the results of the stability monitoring program and any adverse trends;
- Complaints and/or adverse events: a review of all quality-related complaints and the investigations performed at the time;
- Recalls: a review of all quality-related recalls and the investigations performed at the time;
- Review of past PQR responses: a review of adequacy of any other previous product process or equipment corrective actions;
- Post-marketing commitments: for new Marketing Authorisations and variations to Marketing Authorisations or a review of post marketing commitments (if any);
- Equipment qualification: the qualification status of relevant equipment and utilities product related (e.g. HVAC, water, compressed gases, etc.)
- Contractual agreements: a review of any contractual arrangements to ensure that they are up to date. (37) (38)

The collected data should be trended and analyzed to determine if the process is under control, if is capable and to assure the maintenance of validated status. Through trending can be established/revised in-process controls and can also be determined the appropriateness of current specifications both for starting materials and finished product. In addition, it is important to highlight any trends observed and to identify product and process improvements. Improvement plans and actions should be initiated and taken if the process is found to be out of control or has low capability indices.

Working experience

At Bluepharma PQRs preparation is responsibility of Product Quality & Compliance team (previously Quality Assurance team). PQ&C is responsible for collecting all relevant data, documents and information, however, summaries of results, recommendations, corrective actions and conclusions reflecting the data, evaluations and results authorisations, can be provided by other departments.

PQ&C is responsible for assuring that all provisions of the internal respective Standard Operating Procedures are fulfilled, for coordinating the collection of data and information required, solicit all the PQR approvals and coordinate and assemble all corrective actions. The PQR´s are revised by Product Quality & Compliance members and are approved by Product Quality & Compliance Manager/ Qualified Person or her delegate. The final PQR´s are available for consultation in the intranet to all Bluepharma´s departments. Bluepharma´s PQRs are divided in twelve sections, according with related guidelines:

- **Raw materials/packaging materials:** summary of the data concerning all raw materials/ packaging materials used in the production /packaging of the product under review will be done. It includes code number, supplier, manufacturer and batch numbers used. In the annex the relevant analytical data of the Drug Substance is shown and the results obtained for the Assay analyses are graphed in order to easily recognize the variations of this parameter between batches.
- **Critical in-process control and Quality control results**: results from the in process controls, performed by production during the process, are shown in tables as well as all critical parameters in its production. The sets of In-process controls results are graphed in order to easily recognize the behavior of the batches throughout the processes considered. The tables and graphics used on the bulk review vary according with the pharmaceutical form (tablets, Certificate of Analysisted tablets and capsules) and critical parameters evaluated

(individual weight, thickness, hardness, length/diameter, disintegration, friability, average weight and weight of 10 tablets, disintegration, closure/visual aspect). Whenever possible limits/reference values of these parameters are mentioned. The partial and final yields of process are also indicated and analysed. Also, whenever is possible, the data of the critical analytical parameters (assay, dissolution and impurities) is graphed in order to easily recognize the variations between batches and evaluate the compliance with the specifications.

- **Batches failures and reworking/ repacking:** the number of batches released and failed is presented and in case of batch failure, the reason to this event is stated as well as a summary of the performed actions. Also all repacked or reworked batches are mentioned, if any.
- **Deviations, non-conformities, Out of Specifications and Out of Trends:** description of all significant deviations, non-conformities, Out of Specification and Out of Trends during production, packaging and analysis, their related investigations, follow-up and conclusions. If applicable, corrective or preventive measures are indicated. If possible, the manufacture/packaging deviations reported are represented graphically in order to identify recurrent problems and subsequently allowing the proposal of actions for its reduction.
- **Changes to processes, analytical methods, equipment and related documents**: include an overview of all changes to processes, analytical methods and documents associated (manufacturing and packaging protocols, analytical protocols and specifications and approved models), used or not, concerning the product under review.
- **Marketing authorisation variations submitted during the review period:** this is Marketing Authorisation Holders (MAH) responsibility. As contract manufacturers this point is not detailed in Bluepharma´s PQR.
- **Stability studies:** The responsibility of this point is from MAH but Bluepharma as a manufacturer performs stability tests. The results are normally presented separately in a Stability Report. In this PQR section a review of the stability results and adverse trend analysis is presented. It is also stated if the results have been compliant with what is specified and if the expiration date defined is in accordance with the stability results collected during the period under review.
- **Returns, Complaints and Recalls:** if any, every batch recalled, withdrawn from the market or any regulatory alert during the period under review must be listed on the PQR along with

the reason for the withdrawal or recall. Technical complaints received during the period under review are also listed and its evaluation and conclusions are also presented.

- **CAPA´s assessment and effectiveness:** include a review of all deviations and other occurrences reported during the period under review that lead to CAPA, as well as an evaluation of the impact and effectiveness of previous year implemented CAPA´s, if any.
- **Post Marketing commitments**: this section is intended to confirm if any post marketing commitments has been fulfilled but this is a MAH responsibility, therefore is not detailed in Bluepharma´s PQRs.
- **Qualification status of relevant equipment and utilities**: this section is intended to present a summary of the qualification status of Manufacturing/Packaging equipment used concerning the product under review as well as other relevant equipment (heating, ventilating, and air conditioning, compressed air and purified water systems). Any deviation to the Annual Validation Master Plan must be indicated in this section.
- **Quality Agreement:** This section should summarize the terms of the Technical Agreements established between contract giver and the contract acceptor that refer to bulk/finished products. Those contracts should assure that the manufacturing, packaging and/or testing is in accordance with the GMP guidelines and other legal requirements, including marketing authorisation. In this section it will be confirmed if all activities and responsibilities written are being fulfilled and if the Technical Agreement is up to date. Quality Agreements established with suppliers of drug substances and critical excipients, should also be checked for compliance and updated information. This data shall be provided by Quality Management department to the person in charge for the PQR.

To fill in the sections described above, all documents which directly or indirectly refer to the manufacture, control or monitoring of a preparation in the period concerned must be analyzed. These include:

- Manufacturing and packaging batch records and deviation reports (if any)
- Raw materials/ packaging materials data (batch, manufacturer, supplier)
- Specifications and Analytical Procedures (raw materials/ packaging materials/ bulk/ finished product)
- Certificates of analysis (raw materials/ bulk/ finished product), Out of Specification reports and Out of Trends (if any)
- Stability data and Out of Specification reports (if any)
- Status of qualification/ validation of equipment and utilities

- Marketing Authorisations submitted, approved or rejected
- Quality deviations
- Complaints and Recalls
- Quality Agreements

While preparing PQRs I had the opportunity to know in detail all these documents and make a critical analysis over it and thus acquire a more comprehensive knowledge of the product, since the entry of raw materials, through product release, to customer satisfaction.

I also had had the opportunity of update the internal Standard Operating Procedures of PQRs, according to recent updates of relative Guidances and with some related observations of clients during audits.

2.1.2. Analytical Documentation

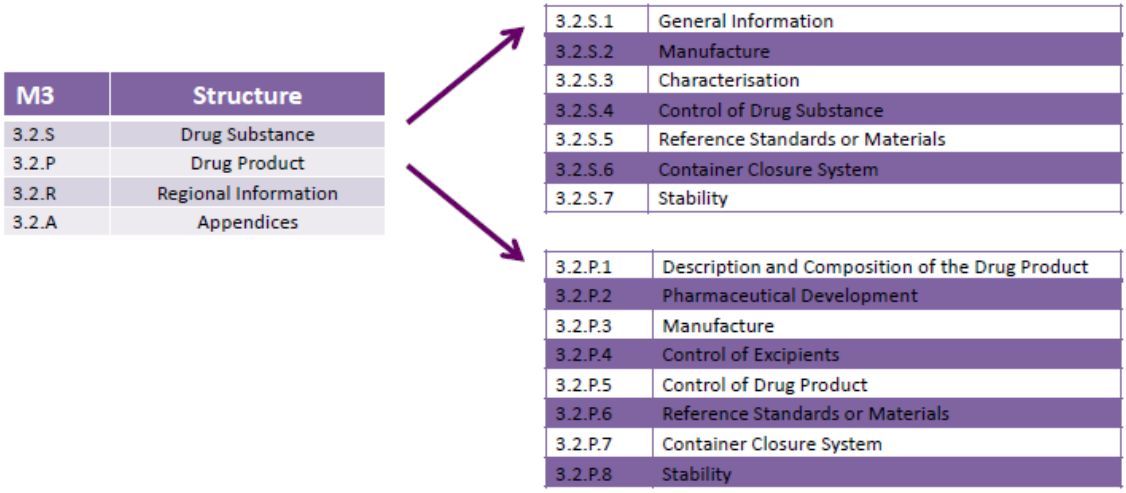
Overall requirements

Through its shelf life period a medicine product must conform to certain limits. To ensure compliance in practice is essential not only to have robust and in control manufacture processes, but also to have traceable quality control measurements systems. Storage conditions must also be under control.

According to 21CFR211.160 (PART 211 -- CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS Subpart I--Laboratory Controls) “laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.” (39)

To set the quality level of the medicinal product for marketing, specifications, i.e. qualitative and quantitative parameters, related test procedures and acceptance criteria are stablished in the dossier for a marketing authorisation. The medicinal product must comply with this data at release and along its intended shelf life. (40)

Chemical, Pharmaceutical and Biological documentation is provided by **Module 3** of the CTD whose structure is detailed on the following figure 3.



M3	Structure
3.2.S	Drug Substance
3.2.P	Drug Product
3.2.R	Regional Information
3.2.A	Appendices

3.2.S.1	General Information
3.2.S.2	Manufacture
3.2.S.3	Characterisation
3.2.S.4	Control of Drug Substance
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability

3.2.P.1	Description and Composition of the Drug Product
3.2.P.2	Pharmaceutical Development
3.2.P.3	Manufacture
3.2.P.4	Control of Excipients
3.2.P.5	Control of Drug Product
3.2.P.6	Reference Standards or Materials
3.2.P.7	Container Closure System
3.2.P.8	Stability

Figure 3. – CTD Module 3 structure (41)

For the purpose of this thesis only sections Control of the Drug Substance (3.2.S.4), Control of Excipients (3.2.P.4), Control of Drug Product (3.2.P.5), and Stability of Drug Product (3.2.P.8) will be further detailed.

Control of the Drug Substance

The documents relating to the active substance present in module 3 includes the information provided by the manufacturer, through *a European Drug Master File* currently renamed as *Active Substance Master File* (EDMF/ASMF) or a *Certificate of Suitability to the Monographs of the European Pharmacopeia* (CEP). The EDMF/ASMF is a document prepared by a Drug Substance manufacturer and submitted solely at its discretion to the appropriate regulatory authority in the intended drug market. The document provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The EDMF/ASMF filing allows a firm to protect its intellectual property from their partners while complying with regulatory requirements for disclosure of processing details. The EDMF/ASMF is subdivided into two parts: Applicant's Part (also referred to as "Open Part") and a Restricted Part (also referred to as "Closed Part"). Only the *Applicant's Part* is available to the pharmaceutical entity that submits the application. The restricted part is available directly to the Competent Authority not being available for accessibility for the marketing authorisation holder. The CEP is a certificate granted by the Certification Secretariat of the EDQM that provide proof that a(n) (active) substance, manufactured in a specific site in accordance with the production process submitted by the manufacturer, can be properly tested and

inspected for quality, with monographic tests. Unlike the EDMF/ASMF, a CEP can be requested not only for any type of active substance but also for excipients. The CEP is optional and not a mandatory requirement in Europe for marketing substances. Nevertheless, it is the preferred option since authorities will generally accept this as proper proof of the active substance quality in marketing authorisation proceedings since it is issued as a result of an inspection performed by EDQM to the manufacture specific site. (42)

The CTD sections concerning the drug substance (3.2.S) may be repeated if the product contains more than one active substance. (43)

Control of Excipients

Excipients are the constituents of a pharmaceutical form apart from the active substance. Include for e.g. fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances etc., as well as the constituents of the outer covering of the medicinal products, e.g. gelatine capsules. (44)

The Control of Excipients is described in the 3.2.P.4 section and includes specifications (3.2.P.4.1) and, where appropriate, includes also the analytical procedures used for testing the excipients (3.2.P.4.2) and the justification for the proposed excipient specifications (3.2.P.4.4).

The excipient used in a given formulation may be:

- described in monographs of the European Pharmacopoeia (Ph.Eur. or EP) or in the pharmacopoeia of an EU Member State;
- described in monographs of third country pharmacopoeias (e.g. United States Pharmacopoeia/National Formulary - USP/NF and Japanese Pharmacopoeia); or,
- not described in any pharmacopoeia.

When described in the EP or in the pharmacopoeia of an EU Member State a reference to the “current edition" of the pharmacopoeia should be included in the dossier. If tests other than those mentioned in the pharmacopoeia are used, proof should be supplied that the test methods are at least equivalent to those described in the pharmacopoeia. It may be necessary to add tests and acceptance criteria to the pharmacopoeial specification, depending on the intended use of the excipient (functionality-related characteristics). Where an excipient is neither described in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted provided that the applicant justify the reference to such pharmacopoeia and submit justified specifications in accordance with the

general monograph of the European Pharmacopoeia. For excipients not described in any pharmacopoeia an appropriate specification for the excipient should be established; this specification must be based on physical characteristics, identification tests, purity tests (including limits for total and individual impurities), assay or limit tests if necessary and corresponding validation parameters, and other relevant tests (e.g. on quantitative parameters which have demonstrated to influence the performance of the dosage form. (44)

Justification of a specification takes into account the choice and particular use of the excipient. For excipients described in the European Pharmacopoeia, or in the pharmacopoeia of an EU Member State, justification of specifications will normally not be required. However, any particular acceptance criteria concerning the characteristics, as defined in Section 3.2.P.2.1.2, should be justified (e.g. particle size testing of a micronised substance). In addition, justification of a specification is not systematically required for well-known excipients (e.g. excipients which have been used in similar medicinal products for a long period of time). Where critical, the justification of specifications should provide information on excipient characteristics relevant to the medicinal product performance (Functionality related characteristics). (44)

In general it is not necessary to carry out identity testing and an assay of the excipients in the medicinal product at release (except for situations envisaged in the Note for Guidance on Specifications: *Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (CPMP/ICH/367/96)). Since the maintenance of the physico-chemical properties of the medicinal product is partly dependent upon the properties and the stability of the excipients it should be ensured that antimicrobial preservative and, if appropriate, antioxidant levels are quantified periodically throughout the shelf-life according to
current CHMP/ICH stability guidelines. (44)

Control of Drug Product

The information included in Module 3 for the finished product (3.2.P), refer to the qualitative and quantitative composition, manufacturing process, quality tests performed, information about containers and stability data to support the proposed shelf life. (17)

The information on quality tests comprise specification(s) of the finished product (3.2.P.5.1), analytical procedures used for testing the drug product (3.2.P.5.2), the validation of Analytical Procedures (3.2.P.5.3) including experimental data for the analytical procedures used for testing the drug product, a description of batches and results of validation batch analyses (3.2.P.5.4), characterisation of impurities (3.2.P.5.5) if not previously provided in "3.2.S.3.2 Impurities", a

justification for the proposed drug product specification(s) (3.2.P.5.6) and reference standards or materials used for testing of the drug (3.2.P.6) if not previously provided in "3.2.S.5 Reference Standards or Materials".

The analytical methods described in the various sections must have a level of detail such as that enables its reproduction by official laboratories. All tests must be validated in accordance with “ICH QA(R2) - Validation of analytical procedures” and the validation results should be made available. (43)

Specification are defined in the ICH Q6 as a “list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use". Specifications are, therefore, one part of a total control strategy designed to ensure product quality and consistency. Conformance to specifications means that a specific material, when tested according to the detailed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards, proposed and justified by the manufacturer and approved by regulatory authorities. Since specifications are meant to confirm quality its content is focused on those characteristics found to be useful in ensuring the safety and efficacy of the drug product, rather than to establish full characterization. (45)

In order to determine the specifications of the finished product, parameters related to the manufacturing process should be taken into account. An appropriate specification for the parameters studied during the phase of development and during the validation of the manufacturing process should be determined. At least those aspects considered to be critical should be the object of specifications routinely verified. (40)

The description of the dosage form, the identification of the drug substance(s) in the drug product, the assay of the drug substance(s) in the drug product and impurities (including degradation products addressed in the “Q3B(R2) - Impurities In New Drug Products” and residual solvents) are considered generally applicable to all drug products. In addition to these tests, other may be considered on a case by case basis for drug products, for e.g. for tablets and hard capsules it can be included the dissolution, disintegration, uniformity of dosage units, water content and microbial limit tests. (45)

Periodic or skip testing may be applicable to some tests as, for example, residual solvents and microbiological testing for solid oral dosage forms. This consists on the “performance of specified tests at release on pre-selected batches and / or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still must meet all

acceptance criteria established for that product". Since this represents a less than full schedule of testing it should be justified, presented to and approved by the regulatory authority prior to implementation. This concept should generally be implemented post-approval since there is limited data available at the time of submission of an application. (40) (45)

Different acceptance criteria for release and shelf-life specifications can be applied to drug products. The applicant proposes a shelf life for the medicinal product mainly on the basis of the level of active constituents (efficacy) and the admissible level of any breakdown products or impurities (safety) and consistent pharmacotechnical properties. From the behaviour of the medicinal product the applicant deduces the appropriate storage conditions which will maintain compliance with the specifications of the medicinal product. The specification limits of the finished product at the time of batch release are set by the marketing authorisation applicant such that the specifications proposed for shelf life are guaranteed and are established on the basis of a critical detailed review of the data gathered from the batches analyzed. However, specifications of the finished product at manufacture may be different from those of the medicinal product at shelf-life due to the fact that, in certain cases, some characteristics of the medicinal product (e.g. assay and impurities) may change during storage under the approved conditions, like impurities and pharmacotechnical properties; therefore, the quality required at the end of shelf life should be taken into account in determining appropriate specifications at the time of manufacture. In Japan and the US, this concept may only be applicable to in-house criteria, and not to the regulatory release criteria. Thus, in these regions, the regulatory acceptance criteria are the same from release throughout shelf-life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf-life. In the European Union there is a regulatory requirement for distinct specifications for release and for shelf-life where different. (40) (45)

Stability of Drug Product

Stability testing is performed to provide evidence on how the behavior of a drug substance or drug product varies over time under the influence of environmental factors such as temperature, humidity, and light. It is also important to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. (46)

ICH Q1A guideline is the ICH guideline where is defined the stability data package for a new drug substance or drug product sufficient for a registration application within the three regions of the EC, Japan, and the US. Tests conditions defined in this guideline are based on an analysis of the

effects of climatic conditions in these three regions and therefore this guideline do not necessarily cover testing for registration in or export to other areas of the world. Besides the world can be divided into four climatic zones, I-IV, based on climatic data, this guideline only addresses climatic zones I and II. It was established that stability information generated in any one of the three regions, EC, Japan and the US, would be mutually acceptable to the other two regions, provided that the information is consistent with ICH Q1A guideline and the labeling is concordant with national/regional requirements. (46)

Two different types of stability studies can be performed along the medicine life-cycle:

- real time stability studies
- accelerated stability studies

In real-time stability studies, a product is stored at recommended storage conditions and monitored until it fails the specification. In accelerated stability studies, a product is stored at elevated stress conditions (such as temperature, humidity, and pH). (46)

In the development phase accelerated stability tests are performed in order to select adequate formulations (from the viewpoint of stability) and container-closure systems by comparing different alternatives. Once the final formulation and manufacturing process have been established, the drug product undergo a series of accelerated stability tests to predict its shelf-life and storage conditions. For confirmation purposes real-time studies must be started at the same time. Since the drug regulatory authority will require information on the stability of the final product, in the final container and packaging, at registration should be presented the data from both accelerated and real-time studies. With regulatory approval, is often established a provisional shelf-life period, provided that the owner of the dossier commits itself and signs a declaration stating that the necessary studies will be continued and completed and that the respective results will be submitted to the registration authority. In the post-registration period, real-time stability studies must be carried on by the manufacturer to substantiate the expiry date and the storage conditions previously proposed and all the data obtained must be submitted to the registration body. Other results of on-going stability studies can be verified in the course of GMP inspections. National health authorities should also monitor the stability and quality of preparations on the market, through a follow-up inspection and testing programme, to ensure its quality and safety of products. Whenever major modifications are made to the formulation, manufacturing process, packaging or method of preparation additional stability studies are required and the results of these studies must be communicated to the competent drug regulatory authorities. (47)

Given all the previous assumptions, the section of Stability Data of Module 3 must include: a stability summary and conclusion sub-section (3.2.P.8.1), where are summarized the types of studies conducted, protocols used, results of the studies and conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life; a post-approval stability protocol and stability commitment (3.2.P.8.2); a stability data sub-section (3.2.P.8.) where should be presented, in an appropriate format (e.g. tabular, graphical, narrative), stability studies, information on the analytical procedures used to generate the data and validation of these procedures; finally information on characterization of impurities is included in the sub-section 3.2.P.5.5. (43)

Working experience

PQ&C department has the responsibility of preparing/revising Analytical Documentation concerning products that already have a marketing authorisation. This includes specifications of excipients, drug substances, packaging materials, bulk product and finished product, and related analytical protocols.

The preparation of analytical documentation of raw materials or packaging materials used in the R&D projects is also PQ&C´s responsibility.

My function concerning analytical documentation has been focused in the preparation and review of specification of excipients, drug substances and bulk product and their related analytical protocols, when applicable.

Internal Specifications serve as base for Quality Control analysis of tests results and approval of batches and therefore must be updated as well as the internal related protocols, when existent.

Excipients specifications may be divided in specifications based on official monographs and specifications based on the manufacturer's documentation. Monograph specifications correspond to the majority of the specifications of excipients. May be based in official monographs of the European Pharmacopoeia (Ph.Eur.), in the American Pharmacopoeia (USP/ NF) or based on both, according to the market to which is intended the final product. For these specifications there is no need to prepare a related analytical protocol since the analytical methods to be used are described in its correspondent monograph. Periodically are published and implemented new volumes or supplements of the EP and the USP/NF. Therefore, all Bluepharma´s excipients specifications based on monographs are reviewed periodically, to check if the new editions/supplements introduce any changes on it; a new edition of the document is issued internally on every review.

The new volumes and supplements are published a few months before the date of its implementation allowing an early evaluation of impact and the implementation of internal updated specifications at the edition or supplement´s implementation date. In order to easier this task, for each edition / supplement of Ph.Eur. and of USP/NF, are published in advance lists with texts, chapters and monograps revised, corrected or new (Contents of Supplement for the Ph.Eur. and Admissions and Annotated Lists for the USP/NF). Some of the changes described on these lists are to be take into account at the publication date of the volume/ supplement (eg the "corrected Texts" of Ph.Eur.). For raw materials that don´t have a correspondent monograph neither in the Ph.Eur. or in the USP, is prepared a specification and a related analytical protocol based on the information provided by the manufacturer (Technical Data Sheet).

As it is for excipients, Drug Substances (DS) can have an official pharmacopoeia monograph associated or not. When there is an official monograph published, the manufacture of that DS can apply for a CEP. If the manufacturer demonstrate that their product complies with the quality standards required by the Ph. Eur. and European regulations, is suitability to be controlled according to the Ph. Eur., complies with the relevant GMPs (GMP) and if the manufacturer accept a site inspection at any time at the request of the EDQM, this entity issue a CEP. This certificate can be included in the CTD application easing the DS use approval by the competent authorities since it constitutes a proof of its quality.

The specifications and related analytical protocols used to control a given DS at receipt in Bluepharma must be, in any case, compliant with the content presented in the 3.2.S.4.1 and in the 3.2.S.4.2 of the CTD, respectively, or on equivalent sections of the ANDA. When a CEP is included in the section 3.2.S.4.1 there is no need to elaborate a related analytical procedure, provided that is made a reference in the internal specification to the monograph that should be followed and are included additional tests described in the CEP (e.g. residual solvents and impurities), in annex. For DS that doesn´t have a CEP a specification and a related analytical procedure is prepared, based on the correspondent DMF.

Both for excipients and DS, testing should be performed for residual solvents when production or purification processes of those raw materials are known to result in the presence of such solvents (listed in the ICH Q3C(R5) - Impurities: Guideline for Residual Solvents). That information must be provided to Bluepharma by the manufacturer of the excipient/DS (technical documentation, Certificate of Analysis) so that the limits and methods may be included in the related documentation of that raw material (residual solvents analytical methods are included as annexes for specifications based on monographs).

Bulk specification and analytical procedures must also be necessarily in compliance with the related sections of the CTD (3.2.P.5 for release and 3.2.P.8 for stability) or the ANDA. Specifications of products meant for Europe are prepared including both release and stability limits, since these may differ as mentioned above.

To each bulk product corresponds an analytical procedure where are described the approved methods contained also in CTD (3.2.P.5.) or equivalent section of ANDA. Methods must be validated in Bluepharma´s Laboratories according to the "ICH QA(R2).

The task of PQ&C regarding analytical documentation is not only limited to the preparation of specifications and associated analytical procedures. Is also performed a thorough job of checking the compliance of these documents with the constant updates that are made in the documents used as their basis. In the case of drug substances and bulk specifications, every time that it is submitted and approved by the authorities an amendment to CTD concerning the respective modules of CTD (3.2.S.4.1 and in the 3.2.S.4.2 for drug substance and 3.2.P.5 and in the 3.2.P.8) or the equivalent sections of ANDA, an internal update of the specifications and analytical procedures concerned must be performed accordingly.

Additionally some clients routinely contact the department of PQ&C and request a document signed confirming that our internal documentation is updated, according with the last version approved of the related sections of the dossier.

All the changes performed in our internal documentation must be supported by a Change Control Report, where must be described the change performed, the reason, its impact, the Risks related with that change and a detailed related Action Plan.

2.2. Additional Activities Performed

Additionally to the main tasks described before, I have been giving support to other tasks developed in the PQ&C department. Of the several tasks performed I highlight the support given in the first months to the Qualified Person (QP) on reviewing the compliance of batch related documentation for emission of the Certificate of Compliance (Certificate of Compliance) for Batch Release, the constants support on Audits/Inspections, the attended training and the training given to new employees or colleagues who assumed tasks on which I have confirmed experience.

2.2.1. Support to the QP Batch Release

Overall requirements

All batches of medicines for human use (MHU), medicines for veterinary use (MVU) and experimental medicines must be certified by a Qualified Person or in the case of the US market, the by the Quality Unit, before being approved for sale / supply or for trials in the case of experimental drugs. This certification is designed to ensure that the batch was manufactured, packaged and analysed in accordance with the requirements of the Marketing Authorisation Dossier (MAD) or Abbreviated New Drug Application (ANDA) / New Drug Aplication (NDA) (regulatory compliance), Dossier Project (Product Specification File) Regulatory Documentation approved Good Manufacturing Practices and other applicable legislation.

The verification of all packaging and manufacturing documentation is a responsibility of the respective sectors (sectors responsible or his delegate) but a final assessment is conducted by the Qualified Person (QP) or its delegate in Product Quality & Compliance. Verification of analytical documentation (including calculations) and respective internal approval is the responsibility of the Head of Quality control and the entire procedure is described in an internal Standard Operating Procedure.

After that a compilation of documents concerning the production and / or packaging and analytical control of a product batch must be performed and in Bluepharma this is a responsibility of the QP/PQ&C department. This batch documentation includes:

- Manufacturing documentation: manufacturing batch record and, if applicable, deviation reports;

- Certificate of analysis (Certificate of Analysis) of batches of active substance and, if applicable, Out of Specification reports;
- Certificate of Analysis of bulk product and, if applicable, Out of Specification reports;
- Packing documentation: packing record) and Out of Specification reports, if applicable;
- Certificate of Analysis of finished product and, if applicable, Out of Specification reports;
- In the case of a product destined to the US, are also included certificates of the analysis, of all raw materials contained in the formulation, for confirmation / verification of its analysis under the USP pharmacopoeia.

For each batch all these documents are verified taking into account the data of submission and approval by the authorities (MAD, regulatory documents approved), GMPs and other legislation in force (Compliance). The compliance of the batch is verified and a Certificate of Compliance and Release is issued. The final release of the product is done in the computerized system SAP, by the QP, not being possible to ship the product without this action.

At the same time is sent to the client documentation concerning the approval/ release of the product in accordance with what is defined in the Quality Agreement between Bluepharma and the client.

For internal management, once this process is completed is filled a table with product data, including: product type certificate (Bulk, Finished Product), product name according to SAP (including name, strength, pharmaceutical form and presentation), batch number; quantity, observations (if is a quarantined shipment, if is launch, among others); date of shipping/ certification, direct client´s name followed by the name of the final client.

In Bluepharma the archive of all batch related documentation of medicinal products for human use and investigational medicinal products is a responsibility of the Product Quality & Compliance Department. Batch documentation MHU / MVU should be kept for one year after the expiry of the product in a minimum at least of five years after certification by the Qualified Person, or in accordance with the Quality Agreement signed between Bluepharma and the client. For experimental medicines, the batch documentation should be maintained for at least five years after completion or formal discontinuation of the last clinical trial in which the batch was used.

Working experience

At the time I began my professional experience in Bluepharma, due to a sharp increase in production given a global launch of a new generic, there was a requirement to assist in the task of

support to QP for batch release. I had performed this task for four months, till the admission of new collaborators. Thus this was my first concrete task performed in Bluepharma.

My function was to compile and select all the batch documentation from manufacturing, packaging and quality control departments (product documentation), prepare the Certificate of Compliance and send the approved and selected documents for the client. The Certificate of Compliance is signed by the QP after the verification of compliance of all product documentation that includes: manufacture records, packaging records, quality control records and deviation reports (if any). The documents that support and that must be sent attached with the Certificate of Compliance are compiled according to what is defined in the client´s respective Quality Agreement.

Along with the e-mailing of Certificate of Compliance and associated documentation I was also responsible for sending, when applicable, samples of the product to clients, via a specialized courier company. I also had the responsibility of updating the table where is registered de data of every batch release, archive all the related documents (digital archive in Bluepharma´s intranet) and archive the paper documents batch related.

2.2.2. Audits/ Inspections

Overall requirements

Auditing is a critical function within a pharmaceutical company since this industry in highly regulated. Audits provide information to the Authorities and/or Clients about how effectively the company controls the quality of their processes and products. Therefore is essential the anticipation and verification of all matters that may be raised by the audit authority to ensure greater responsiveness and assertiveness and thus gain the confidence of those entities. Facility audits/inspections can be focused on several points, including:

- Review of facilities for GMP compliance with EMA/FDA regulations and guidelines, International Conference Harmonization (ICH) Guidances and client specifications
- Review all pertinent documents that support GMP and client specifications
- Inspect facilities, equipment, and laboratories
- Assess Quality Systems including all internal Standard Operating Procedures and associated GMP documents
- Assess CAPA programs (Corrective Action/ Preventive Action)

- Review validation of manufacturing equipment, product process, and equipment cleaning
- Assess Vendor Certification Programs
- Review method validation (analytical and microbiological)
- Evaluate data integrity
- Assess qualification and training of personnel
- Assess supplier qualification
- Review Change Control Records, Complaints, Deviations and Out of Specifications.

Audits are followed by the Head of Quality Departments and is crucial the support of their team in the success of the Audit.

Working experience

Bluepharma is a GMP certificated company by INFARMED, I.P and is authorised by the same entity to manufacture different non-sterile products in the following solid dosage forms: capsules, hard shell, tablets, powder and granules. The INFARMED´s Inspection Unit performs regular supervision and inspection activities in Bluepharma´s facilities to check the implementation of best practice systems in accordance with national and international standards established procedures by the European Commission in different areas of intervention by the European Medicines Agency (EMA) and the System International Cooperation of the Pharmaceutical Inspectorate Services (PIC / S).

FDA inspects foreign manufacturing sites for FDA-regulated products that are sold in the United States. FDA conducts several types of inspections to help protect consumers from unsafe products: pre-approval inspection after a company submits an application to FDA to market a new product; routine inspection of a regulated facility (performed every two years) and “for-cause” inspection to investigate a specific problem that has come to FDA’s attention. In 2009 Bluepharma was inspected by the FDA for the first time and obtains official approval for the development / manufacture of solid pharmaceutical forms to be exported to the US market. After that, two more inspections (routine inspections) were performed in Bluepharma facilities.

Bluepharma's main business aims at the integration of the licensing of its in-house developments coupled with the supply of the finished product. Bluepharma collaborates with the major European generic pharmaceutical companies, while distributing medicines worldwide, having a wide range of clients. Being Bluepharma a contract manufacturer and a developer and contract research

company of medicinal products, clients and potential clients audits are a constant. Their satisfaction during the audits is essential for the maintenance of the business already established and to achieve new business opportunities and thus contribute to the company's success.
During my professional experience at Bluepharma I had the opportunity of helping on the preparation and giving support to two Infarmed Inspections and two FDA Inspections and several clients or potential clients audits. I had also the opportunity of performing tasks defined in action plans resultant from questions that arose during the course of inspections / audits.

2.2.3. Trainning

Overall requirements

Employee is the valuable resource for any organization. The success and failure of an organization extremely depends on the performance and productivity of employees. Training enables people to acquire new skills, to enhance their skills and keep them updated with recent changes and therefore has a significant role on productivity, its boosting its increase.

Working experience

Given the various restructurings that were made in the department in which I work, either with the division of quality assurance, or with changes in human resources, it was necessary to readjust tasks and thus have / give training. Giving these adjustments I had the opportunity to train colleagues on tasks for which I was able (previously described as main). I also had the opportunity to give a brief training on these tasks to new employees in order to make them know the work performed in the PQ&C department.

2.3. On-the-job additional learning

Bluepharma is a certified company and consequently the integration of new collaborators comply with certain requirements, in particular training/information sessions concerning the main rules and principles of different areas of the company. Therefore, in the first days at Bluepharma, in order to acquire knowledge in general areas that were transversal to all company departments, I had to read the company's Site Master File and also relevant Standard Operating Procedures for my future functions. I also had to attend training sessions concerning general issues applicable to the entire company. From these I highlight the following:

- "Welcome" manual
- Bluepharma Quality Management System
- Environment and Safety Management System
- GMPs
- Innovation and R&D certification
- Information technology services

Throughout last year's Bluepharma gave me also the opportunity of attending different types of training sessions. Some of them were general and mandatory for all collaborators; others were specific and intended to provide knowledge in specific issues related with new tasks to perform. From the last ones I highlight, among others, the sessions on GMP continuous learning, sessions concerning CTD contents and regulatory requirements, Out of Specification / Out of Trend, new legal requirements on active substances, deviation reports management and change control management regarding documentation.

Those training sessions were very useful to refresh some concepts learned in my academic journey as well as to acquire new concepts, such as GMP, Quality systems and national and international regulations and guidelines.

I have also attended some additional brief formative sessions (previously named "paper clubs" and now "Forum of Innovation and Quality"), which addressed different knowledge areas around the pharmaceutical industry and other internal seminars regarding relevant company related issues for workers clarification.

3. Discussion

A work experience at a Quality Assurance/ Product Quality & Compliance department of a Pharmaceutical Industry provides the opportunity to perform several different activities and gain a more comprehensive understanding of the company, of the activities developed in the different departments and of the interactions established between them.

At Bluepharma my working experience started to be focused on support to batch release, followed by Product Quality Reviews preparation and finally has been directed to the preparation and compliance verification of analytical documentation.

Qualified Person is responsible for the release of the product to clients/ clinical trials. The product only can be released after a proper review of the batch documentation (production and packaging records and deviation reports, if any), and if the quality control testing data confirm that the product meets specifications. If there is some deviation that can affect the quality, safety and efficacy of the product, the batch must be rejected and an investigation must be performed to find the root cause of the problem occurred. The batch release is, therefore, an activity of great responsibility and the utmost importance for the company. On Quality Agreements are detailed several requirements concerning the documentation batch related that must accompany the Certificate of Compliance. This way, the support provided to the emission of the Certificate of Compliance is of great importance to ensure clients satisfaction and compliance with those requirements. While performing this task I was able to collect, compile and archive batch manufacturing, packaging and quality control documentation, compile the “Release Documentation” and deliver it to the client. This task was a very enriching experience, first of all due to the fact that, till then, I did not have previous experience in the Pharmaceutical Industry area; by performing it, I had the opportunity of become familiarized with the manufacturing, packaging and quality control documentation as well as become aware of the requirements that must be fulfilled in order to release a batch for the market. By accomplishing this task I realized that this is not always easy, since there are deadlines to release and ship the product to customers and the execution of PQ&C functions is dependent on the flow of documents between the different departments involved.

PQRs are an effective quality improvement tool to enhance the consistency of the processes and the overall quality of the product since it provides a broader view of product data, and enables the capture of trends and help to determine the need for revalidation and changes, if needed. PQR´s can be considered as a continuous validation of the product during its life-cycle. The PQR´s task

comprise the collection of all manufacturing, packaging and quality control data, deviation and Out of Specification reports, stability data and Quality Agreements, the analysis of trends and processing of batch related data, the draft of the report itself; the delivery of it to the client and, if requested, the clarification of their doubts. While preparing PQRs I have been giving the opportunity to know in detail all the product related documents, to make a critical analysis over it and thus acquire a more comprehensive knowledge of the product and of all the processes needed to obtain it, since the entry of raw materials, passing through product release, to customer satisfaction. I consider the preparation of PQR´s a very challenging task, not only because it gives me a tremendous knowledge on the pharmaceutical industry reality but also for its enormous importance in assessing the quality of the product and promoting their continuous improvement and thus higher client's satisfaction.

Quality control is a procedure or set of procedures through which is ensured that all the materials, intermediate products and the finished products comply with a defined set of quality criteria or meets the requirements of the client (according to the Marketing Authorisation dossier). Since drug products must be marketed as safe and its performance must be consistent and predictable quality control is an essential operation of the pharmaceutical industry. Of great importance are also the documents used as a basis and guidance to these tasks undertaken in quality control department, such as the specifications and related analytical protocols. At Bluepharma the preparation, review and update of specifications and analytical protocols for excipients, drug substances and bulk product is QP&C responsibility as well as the assessment of compliance of that documentation. Given the huge amount of excipients and active substances used, the diversity of products that are produced and the variety of customers with different Marketing Authorisations, the preparation of analytical documentation and the verification of its compliance is undoubtedly a very challenging task and requires tremendous work and constantly updated to ensure compliance. This task is also quite rewarding once there is a permanent involvement of other departments, including the quality control, stability department and regulatory affairs, enabling me to acquire new knowledge every day.

Auditing is a critical function within a pharmaceutical company since it provides information to the Authorities and/or Clients about how effectively the company controls the quality of their processes and products. Support tasks performed before and during inspections/ audits are therefore of extremely importance to ensure greater responsiveness and assertiveness and thus gain the confidence of the inspectors/auditors. This task was very enriching, not only because it confronts us with the huge level of requirements of the inspection and audit entities as well as it continuous

alert us to numerous points for improvement, even when the audited company is governed by high quality standards and complies with all its legal obligations, as in the case of Bluepharma.

All these hard skills described above enabled me to deepen my knowledge about the structure and functioning of a Pharmaceutical company and continually update my knowledge on ISO standards, GMP's and other regulations with great impact on the company. Besides the tasks described above, I was also able to:

- elaborate and review Standard Operating Procedures applicable to the PQ&C department or related with its functions;
- perform all procedures related to the preparation, review, approval and document distribution;
- reply to requests for clarification or doubts raised internally or by customers in relation to specific tasks performed or general questions related to Product Quality and Compliance;
- provide training to colleagues and new collaborators.

Training sessions were also very useful to refresh some concepts learned in my academic journey as well as to acquire new concepts, such as GMP, Quality systems and national and international regulations and guidelines.

Along my professional experience at Bluepharma I have been giving also the opportunity of developing and improving some soft skills. Responsibility sense was definitely one of the soft skills more enhanced during this experience since the activities performed in the PQ&C department are of extreme importance and have a high impact on the company. All activities must be performed with high precision and accuracy. Thus I had to learn to be more careful in the execution of my duties, even in the simplest ones. The existence of deadlines and the development of different tasks determined the development of time management and organizational skills. I have learned to plan my work day in advance and organize my tasks according to their priority, and thus carry them all quickly and efficiently. I also have learned how to deal with unforeseen circumstances that force me to change my plan and reorganize my tasks in order to not jeopardize the deadlines. I also have developed my verbal and written skills, including in English. This learning is important not only to prepare documents but also to present and discuss ideas on an assertive way. I also have improved my self-assessment capacity, in order to understand why mistakes occur, what can be improved, and how; I have also developed my autonomy, my capacity of critical thinking and problem solving and my team work ability.

Some of these learnings were previously acquired throughout life and with my previous academic and professional experiences. However, this professional experience confronted me with new situations and allowed the development and improvement of all these skills. For that, was crucial the support of my work colleagues and the orientation of the person responsible for the QP&C department.

Along my journey at Bluepharma I have also faced some difficulties, mainly due to several restructuring of the department over this period with consequent reorganization of tasks. Another difficulty identified in the performance of my duties is related with the communication between departments that sometimes tends to hinder the realization of the tasks on time.

Therefore, this professional experience was not always a simple process, however it has been always a very challenging experience that made me a more versatile and flexible person and that continuously provide me the opportunity of acquire knowledge in different areas of the pharmaceutical industry.

4. Conclusion

This thesis intends to present the necessary steps for develop professional experience on Product Quality and Compliance in a Pharmaceutical Industry. In this case reflecting my personal experience, by describing the activities performed and the learnings and skills acquired, as well as highlight the importance of the work developed in this department and its contribute to the good performance of the company and to the achievement of their objectives and mission.

Working in this field gives to the professional the opportunity of gaining a broad understanding of the pharmaceutical industry, pharmaceutical quality systems and the drug development process. In my case it allowed me to refresh theoretical knowledge acquired during my degree in Pharmaceutical Sciences, as well as in my Master's Degree in Pharmaceutical Biomedicine and also gave me the possibility to reflect on my weaknesses and strengths and of developing my capability to handle with stressful and challenging real life situations, forcing me to improve the less positive aspects every day.

The activity of a Product Quality and Compliance department is transversal to the entire company involving constant communication with all company departments. QP&C department of Bluepharma is responsible for the preparation of the documents product related necessary for development and routine production as well as for the documents required to control and monitoring the majority of the processes, and therefore its role in the company is crucial to development of the activities of the company and the achievement of their objectives and quality standards of excellence.

The tasks that I have been performing are just a small part of the entire work developed in this department but highlight its crucial role on maintaining and assure the quality standards required in the pharmaceutical industry.

Working on Product Quality &Compliance provides every day the opportunity to influence working practices in order to improve standards of quality, that include the commitment to GMP and an integration of their requirements into the tasks for which I am responsible.

The performance of my duties in the Product Quality &Compliance department has been a very enriching experience since I am constantly developing my knowledge and skills and I am confronted every day with new challenges. All these challenges that I underwent through enabled my professional and personal growth always towards a continuous improvement.

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