Universidade de Aveiro Secção Autónoma de Ciências da Saúde
2013

NÁDIA LIBÂNIA LOPES FERNANDES

RELATÓRIO DE ESTÁGIO: EXPERIÊNCIA DE 11 MESES EM FARMACOVIGILÂNCIA

INTERNSHIP REPORT: A 11-MONTH EXPERIENCE IN PHARMACOVIGILANCE

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Relatório apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica do Professor Doutor Sérgio Paulo Magalhães Simões, Vice-Presidente da Bluepharma - Indústria Farmacêutica, S.A. e Professor Auxiliar com agregação da Faculdade de Farmácia da Universidade de Coimbra e do Professor Doutor Bruno Miguel Alves Fernandes do Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

Dedico este trabalho à minha mãe, mulher coragem, a quem devo grande parte do que sou.

O júri

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palavras-chave indústria farmacêutica, farmacovigilância, assuntos regulamentares, serviço científico, exportação

Resumo

O presente relatório propõe relatar a minha experiência de 11 meses em farmacovigilância na Bluepharma - Indústria Farmacêutica, S.A. O estágio foi realizado no âmbito do mestrado em Biomedicina Farmacêutica e teve como objetivos a aquisição de competências técnicas e de experiência em farmacovigilância e a consolidação de conhecimentos.

No primeiro capítulo é feita uma introdução ao estágio curricular, seguindo-se uma descrição do estado da arte da indústria farmacêutica, focando-se no mercado farmacêutico e no seu ambiente regulamentar na União Europeia, em especial na área da farmacovigilância. Neste capítulo é ainda apresentada a empresa de acolhimento e os objetivos do estágio. No capítulo seguinte são descritas as formações multidisciplinares, bem como as tarefas e atividades desempenhadas durante o período de estágio. No final é apresentada uma discussão e conclusão, incluindo uma análise das atividades desenvolvidas, principais dificuldades sentidas bem como das competências adquiridas durante esta experiência profissional.

keywords

pharmaceutical industry, pharmacovigilance, regulatory affairs, scientific service, exportation

abstract

The present report intends to describe my 11-month experience in pharmacovigilance at Bluepharma - Indústria Farmacêutica, S.A. The internship was performed within the scope of the Master's Degree in Pharmaceutical Biomedicine, aiming to acquire technical skills and experience in pharmacovigilance, as well as to consolidate previous knowledge.

The first chapter introduces the internship and describes the state of the art in the pharmaceutical industry focusing on the pharmaceutical market and regulatory environment in the European Union, especially in the pharmacovigilance area. This chapter also includes a description of the host company and the internship objectives. The subsequent chapter presents a description of the multidisciplinary experience as well as the tasks and activities developed during the internship period. Finally, it is presented a discussion and conclusion, which include a critical analysis of the tasks developed, main difficulties and skills acquired during this professional experience.

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Abbreviations

ACK	Acknowledgement
ADR	Adverse drug reaction
API	Active pharmaceutical ingredient
CA	Competent Authorities
CIOMS	Council for International Organizations of Medical Sciences
CPP	Certificate of a pharmaceutical product
CTD	Common Technical Document
DLP	Data lock point
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EURD	EU reference date
EV	EudraVigilance
GMP	Good manufacturing practices
GVP	Good pharmacovigilance practices
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual case safety report
INFARMED, I.P.	National Authority of Medicines and Health Products, I.P.
IPC	In-process control
ISO	International Organization for Standardization
MA	Marketing authorisation
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
PIL	Patient leaflet
PRAC	Pharmacovigilance and Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic safety update report
EU-QPPV	Qualified person responsible for pharmacovigilance in the EU
R&D	Research & Development
RMP	Risk management plan
RTF	Rich Text Format
SmPC	Summary of product characteristics
SOP	Standard Operating Procedures
WHO	World Health Organization
XEVMPD	eXtended EudraVigilance Medicinal Product Dictionary
XML	Extensible Mark-up Language

1. Introduction

The present work consists of a curricular internship report within the scope of the Master's Degree in Pharmaceutical Biomedicine. The curricular internship occurred at Bluepharma - Indústria Farmacêutica, S.A. from June 2012 to May 2013.

This report describes my working experience during 11 months at Bluepharma Indústria - Farmacêutica, S.A., as well as the learning outcomes and skills acquired during this period.

For these purposes, this report will address the current state of the art in the pharmaceutical industry focusing on the pharmaceutical market and regulatory environment. A brief vision on the institution will be made and as well as the objectives proposed for my internship in the Regulatory Affairs and Pharmacovigilance department.

Then, the multidisciplinary experience that was carried out to understand the objectives and activities performed in each company's department as well as the understanding of how they interact, will be described. It will also be reported the specific experience gained by stating all the activities in which I participated during my internship in the Regulatory Affairs and Pharmacovigilance department.

A brief discussion and conclusion will be presented at the end, discussing the different tasks assigned, the difficulties encountered during my internship as well as the skills developed and their relevance to my academic and professional development.

1.1. 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 in European Union (EU) and pharmacovigilance. These topics are addressed since the main activities developed during my internship were related to the regulatory affairs and pharmacovigilance areas.

Pharmaceutical market

Pharmaceutical industry discovers, develops, manufactures, and commercialises medicinal products which are designed to diagnose, prevent or cure diseases and consequently to enhance health and/or quality of life and prolong the average lifetime [1].

In 2012, Pharmaceutical companies invested an average of more than $1.3 billion developing a single innovative new medicinal product. The research-based pharmaceutical industry contributed to medicinal progress throughout the translation of fundamental research into innovative treatments. The increase in scientific knowledge and the development of new technologies have contributed to improve and maintain health and increase the life expectation [2-4].

According to European Federation of Pharmaceutical Industries and Associations' report of 2012, "the world pharmaceutical market was worth an estimated €614,583 million at ex-factory prices in 2011". The world's largest market remains the North American market followed by European and Japanese [2].

The originator companies spend a large amount of money and time investigating and developing new products. In Europe, innovation is protected at two different parallel levels, by standard commercial laws, through patents and supplementary protection certificates, and by specific "health laws" that specifically govern generic medicinal products development (data protection period of 8 years) and marketing (market exclusivity period of 10 years), since the initial authorisation of the reference product is granted. Generic medicinal products applications can only be submitted to the CA after the data protection period and can only be placed on the market after the market exclusivity period [5].

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 the generics medicines market size was of €31 billion in 2009 [6].

In contrast to the general perception, the generic medicine companies also contribute to innovation. A large amount of generic medicines companies invest a significant amount of their budgets on innovation. This innovation is related to the creation of new strategies to overcome patents that may cover active pharmaceutical ingredient (API) substances or manufacture processes of a finished product, new technologies by means of the improvement of the existing formulations as well as new systems to increase patient compliance [6].

To maintain the sustainability of healthcare systems, one important factor is the cost of medicines. Over the years, pharmaceutical expenditure has been growing in Europe and it is possible to predict that this expenditure will not undergo a reduction in the coming years due to the aging population increase and changes in the European citizens life style [6, 7].

The economic and financial crisis in the EU enhance the need to have effective and efficient healthcare systems and adequate management with the strain resources available [7]. Consequently, the generic medicines play an important role in healthcare systems, treating diseases at lower costs and consequently increasing the accessibility and affordability of essential medicinal products to patients [6].

Despite the advantages presented by generic medicines some companies of originator products, health care professional and patients still do not fully trust this type of medicines, arguing that they may be less safe and effective and have less quality than the branded medicines [8].

Any type of medicinal product can only be marketed in the EU once they have been approved by the European Medicines Agency (EMA) or National Competent Authorities (CA) [9]. Regulatory authorities aim to protect public health, so the generic medicinal products must fulfil stringent and science-based standards of efficacy, quality and safety as an originator medicine in order to grant a marketing authorisation (MA) and ensure that they are not a threat for public health [7, 8].

In order to grant a MA to a generic medicinal product, this must contain the same active ingredient as the originator reference product, be identical in pharmaceutical form, route of

administration and strength, be bioequivalent and manufactured according to Good Manufacturing Practice (GMP) regulations [8, 9].

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, which will be reviewed with the same accuracy than the innovator reference medicinal product already approved [9].

Pharmaceutical Regulatory Environment

Medicinal products are among the most stringently regulated products in the world. Extensive and complex regulations have been developed due to the need of safeguarding public health. Nevertheless, this has not been a simple process. Current regulations were developed overtime, and the huge advances in regulatory development were triggered by adverse incidents [10].

The pharmaceutical regulation is based on four main principles and concepts which are safety, efficacy, quality and risk-benefit [10].

Between the decade of 60s and 70s, it was observed a rapid increase in the regulatory requirements concerning safety, quality and efficacy data of medicinal products submitted to the regulatory authorities. Simultaneously, the pharmaceutical industry started its internationalisation process, seeking new global markets [10]. The internationalisation of the pharmaceutical industry is not a simple process, since pharmaceutical industry finds different technical and administrative requirements from country to country. To market new worldwide products, companies had to duplicate various test procedures, which were time-consuming and expensive [11].

Consequently, an urgent need to harmonise regulation emerged due to several concerns like the over rising costs in health, the increasing costs of Research and Development (R&D) and the delay in the availability of new treatments to patients [1].

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) initiative joins medicinal products regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States and contributes to the harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product development and

registration at an international level. The harmonisation process results from a process of scientific consensus with regulatory bodies and industry working together to the development of ICH Tripartite Guidelines [12].

One of the most important contributes of the ICH was the creation of the Common Technical Document (CTD), through an Industry proposal in 1996. This document revolutionised the submission process for pharmaceutical companies as well as for regulatory authorities. The CTD, and, since 2006 the electronic CTD, allow time and resources saving since instead of multiple complex submissions it is possible to submit a single technical dossier in the three ICH regions [13].

Consequently a new regulatory language was created facilitating simultaneous submission, approval, and launch of new multi-market medicinal products and promoting faster access to life-saving treatments to patients beyond ICH regions [12].

European Legislation

Over the years, stringent legislation and requirements have been developed concerning the R&D of medicinal products, MA approval, promotional practices and monitoring of the safety of medicines during development and post-authorisation phases [14].
The European legislation related to medicinal products for human use is composed by a set of legal instruments, organised hierarchically as presented in Figure 1 [5].

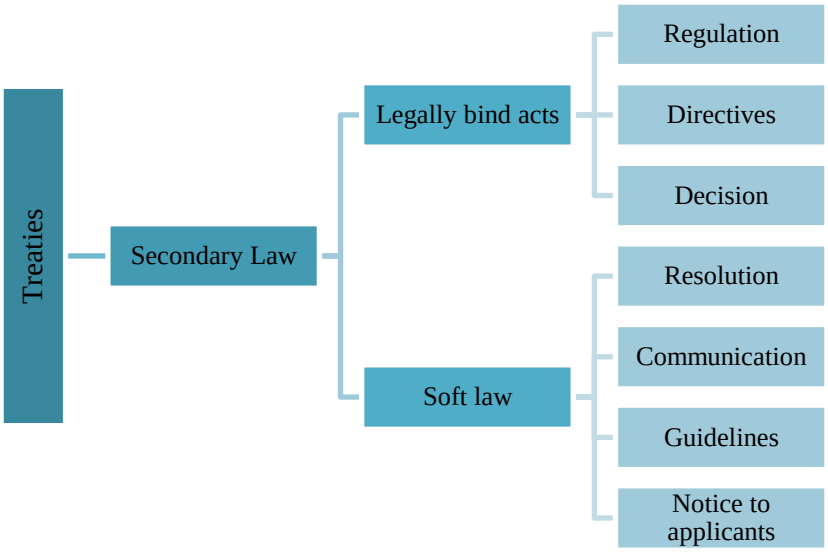

Figure 1 - Overview of the hierarchy of Community texts

The European pharmaceutical legislation is compiled in a set of publications globally named Eudralex. Volume 1 to Volume 5 of Eudralex, compile the body of the EU legislation in the pharmaceutical sector; Volume 1 is related to medicinal products for human use and Volume 5 concerns medicinal products for veterinary use. The basic legislation is supported by a set of guidelines published in the other different volumes (Volume 2 to Volume 10), according to the pharmaceutical area of interest [15].

The main objective of the European Regulation is to safeguard public health. For that, three main areas of activity are taken into attention by the regulatory authorities: product development, product manufacture and market vigilance [10].

Product development – pre-authorisation phase

To commercialise a new product, the company that is developing the product must generate sufficient data to demonstrate the efficacy, safety and quality of the product. This information is submitted to the regulatory authorities for review in the CTD format as referred above [14].

The CTD structure comprises five modules containing non-clinical, clinical and quality information as presented in Figure 2. Module 1 contains the regional and administrative information and it is specific for each region (not being considered part of the CTD). The other four modules are common to the three regions and are in an harmonised format [16].

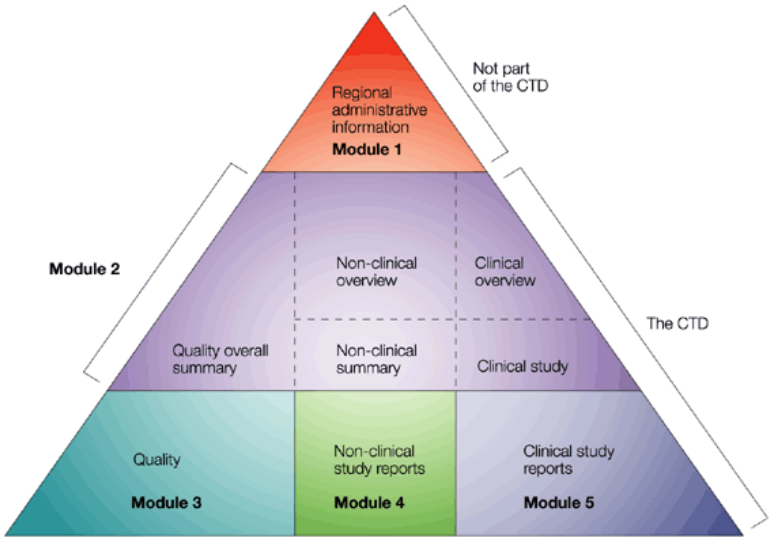

Figure 2 – Common Technical Document reproduced from reference 17

If the information is satisfactory, the regulatory authorities will grant a MA. 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*") [17].

Product manufacture

The manufacture process is also an important area for the regulatory authorities [18]. The pharmaceutical industry activity is governed by a set of norms and procedures of legal framework that constitute the GMP. 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. GMPs cover the following areas:

- Quality Management
- Personnel
- Premise and Equipment
- Documentation
- Production
- Quality Control
- Contract Manufacture and Analysis
- Complaints and Product Recall
- Self-Inspection

All medicinal products manufacturers for human use have the obligation to possess a manufacture authorisation for the manufacturing of their products and a GMP Certificate. These documents are issued by EU National CA after verification and inspection of the activities and procedures implemented in the pharmaceutical facilities/sites [9, 18].

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 [9, 18].

National CA perform regular inspections to the sites in order to verify the compliance with GMP principles and relevant regulatory requirements [14].

Pharmacovigilance

When a MA is granted, it does not mean that the medicinal product does not have any safety issue. It only means that, based on the current scientific knowledge, the benefits outweigh identified risks.

This concept is very well established by a statement of the Committee on Safety of Drugs, which clearly states that "No drug which is pharmacologically effective is entirely without hazard. The hazard may be insignificant or may be acceptable in relation to the drug's therapeutic action. Furthermore, not all hazards can be known before a drug is marketed"[19].

It is recognised that, 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. No long-term treatment data is available and the inclusion criteria is narrow, in clinical trials higher risk subgroups are not included nor patients with concomitant illnesses that require use of other medicinal products. These factors underlie the need for continuing to analyse and assess relevant safety and effectiveness information throughout the medicinal product's lifecycle [14, 20].

According to World Health Organisation (WHO), pharmacovigilance is "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" [21]. The regulatory authorities put in place systems for a systematic collection and assessment of information about adverse drug reactions (ADRs), over the product's lifetime. These systems allow to identify risks that did not surface during the pre-marketing phase and that only are possible to identify in real life conditions [20].

Medicines bring, to patients, many benefits to health such as the improvement of quality of life, prevention of millions of deaths (with vaccination and antibiotics and treatment of cancer and heart diseases') [22].

However, in 2008 the European Commission (EC) published their proposals for strengthening pharmacovigilance framework, concluding that [22]:

- Approximately 5% of all hospital admissions are due to ADRs;

- ADRs are the fifth most common cause of hospital death;
- ADRs cause 197,000 deaths each year;
- In EU, ADRs represent, to society, a total cost of €79 billion.

Indeed, ADRs are associated to high morbidity and mortality being a serious public health issue [22].

To improve the public health protection new European pharmacovigilance legislation was prepared and subsequently adopted in December 2010 and most legal measures began to be applied on 2 July 2012. The new legislation comprises the Directive 2010/84/EU of 15 December 2010 amending Directive 2001/83/EC and the Regulation No 1235/2010 of 15 December 2010 amending Regulation No 726/2004. The Regulation became immediately enforceable in all Member States and the Directive was transposed to the Portuguese National Law by means of the publication of the Decree-Law 20/2013 of 14 February [23, 24]. This change in the European legislation, is considered the biggest change in regulation of human medicinal products since 1995 having an impact on the entire product life cycle [23, 24].

To support the new legislation on pharmacovigilance and to facilitate the performance of pharmacovigilance in EU, a new set of guidelines - good pharmacovigilance practices (GVP) - were developed and, once adopted, will replace the current Volume 9A of the Rules Governing Medicinal Products. In total, there are 16 GVP modules covering all major pharmacovigilance processes. At the moment, most modules are already in force and it is expected that the full set of modules will be available during the present year [23, 24].

The new legislation on pharmacovigilance is focused on [9, 22, 23, 25]:

1. The collection of information concerning the medicinal products based on risk management plans (RMP) (which became required for the submission of all new medicinal products), periodic safety update reports (PSUR) and post-authorisation safety and efficacy studies for which stronger requirements are demanded; ADR reporting by patients (which involves the implementation of direct consumer reporting of suspected ADR systems);
2. The use of the EudraVigilance (EV) database for signal detection through the analysis and understanding of available data and for submission of PSUR, RMP, ADR and information concerning all the medicinal products authorised in the EU;

3. Additional monitoring of medicines through the publication of a list of medicinal products subject to additional monitoring, the addition of an inverted black triangle to the medicinal product's information of the products included in that list with a standardised sentence and the inclusion of a standardised text that encourages ADR reporting for all medicines;
4. Creation of a new EMA's Committee, Pharmacovigilance and Risk Assessment Committee (PRAC), with the objective of promoting and safeguarding public health, reinforcing referral procedures and implementing a robust EU decision-making on safety issues;
5. Increase of the communication and transparency with different stakeholders by mean of the publication of information concerning medicinal products approved in EU, public hearings, as well as, coordination of safety messages between the MS.

National Pharmacovigilance System

In Portugal, the pharmacovigilance system was created in 1992, being the National Authority of Medicines and Health Products, I.P (INFARMED, I.P.) responsible for the coordination of the National Pharmacovigilance System [26]. The National Pharmacovigilance System is formed by the Directorate of Medicines Risk Management, the Regional Pharmacovigilance Units (North Pharmacovigilance Unit, Center Pharmacovigilance Unit, Lisboa and Vale do Tejo Pharmacovigilance Unit and South Pharmacovigilance Unit), healthcare services, including health care professionals and sales representatives, Marketing Authorisation Holders (MAHs) and patients [26].

1.2. Vision on the Institution

Bluepharma - Indústria Farmacêutica, S.A. is a pharmaceutical company based at Coimbra. It was founded in February 2001, with Portuguese capital only, by a group of Portuguese professionals who acquired Bayer's industrial unit.

Bluepharma - Indústria Farmacêutica, S.A. initiated its activity as a contract manufacturing organisation, manufacturing product (bulk or finished product) to other pharmaceutical companies.

As time went by, Bluepharma broaden their horizons and goals and the company's strategy changed and in addition to the production of pharmaceutical medicinal products, they also started investing in the investigation and development of new technologies, starting this activity as a contract research organisation. In 2003, Bluepharma created the department of Research & Development and its first affiliate Bluepharma Genéricos – Comércio de Medicamentos, S.A.

Currently, Bluepharma maintains the manufacturing of medicinal products for other companies and for itself but also develops products/technologies and provides services to different clients. The company offers out-licencing by licencing technologies to other companies according to predetermined rules established in licence agreements and product supply agreements.

The main business activities of Bluepharma are the following:

- Production of medicinal products for other companies;
- Production and commercialisation of own brand of generic medicinal products - *Bluepharma Genéricos – Comércio de Medicamentos, S.A.*
- Research, development and registration of pharmaceutical medicinal products;
- Licensing of new technologies.

Bluepharma is authorised to manufacture different non-sterile products in the following solid dosage forms: capsules, hard shell, tablets, powder and granules. It is a GMP certificated company by INFARMED, I.P., the company obtained an environmental certificate Eco-Management and Audit Scheme and in 2009, became the first Portuguese pharmaceutical company obtaining the Food and Drug Administration certification.

Also, Bluepharma faces the future investing in emerging fields such as oncology, nanotechnology and biotechnology by establishing partnerships with multinational pharmaceutical companies, local and international research centers.

The organisational chart of Bluepharma is presented in Figure 3 [27]. My curricular internship occurred in the Regulatory Affairs and Pharmacovigilance department.

The Regulatory Affairs and Pharmacovigilance department is constituted by six collaborators. The majority of the team elements has a degree in Pharmaceutical Sciences and several years of experience in pharmaceutical industry. Consequently, this was for me a very enriching experience.

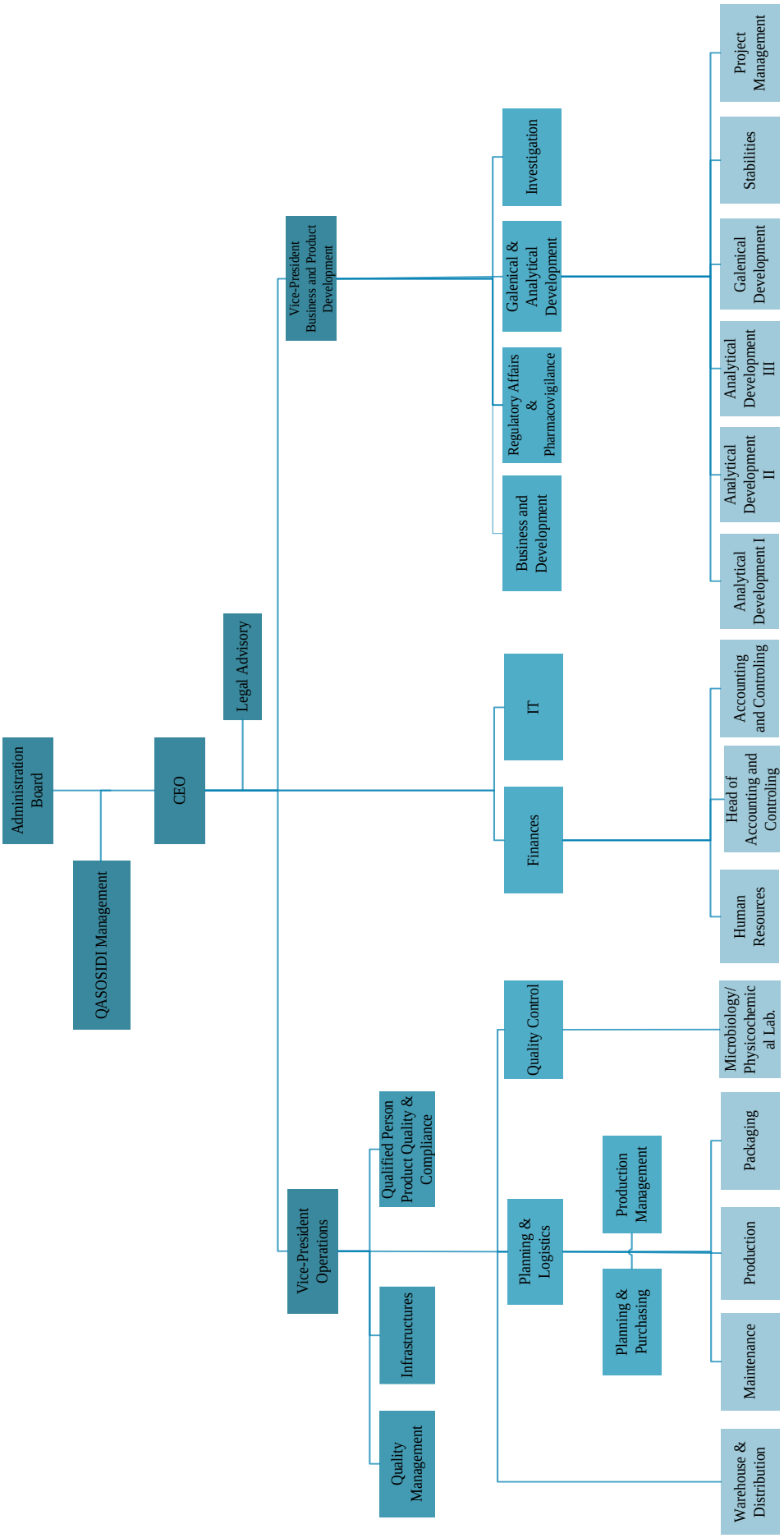

Figure 3 – Bluepharma's Organisational Chart [27]

1.3. Internship Objectives

This internship had the objectives of developing skills/competences acquired during the Degree in Biomedical Science and in the Master Degree in Pharmaceutical Biomedicine and gaining new personal and work capacities and competences. The following objectives were established:

Hard skills

- To identify the organisational structure of Bluepharma and its main areas of activity
- To identify the Regulatory Affairs and Pharmacovigilance structure and its interaction with other departments namely Research & Development, Quality Control, Quality Management and Product Quality & Compliance
- To understand the pharmacovigilance legislation as well as the GVP
- To participate in the preparation and implementation of Pharmacovigilance System Master File (PSMF)
- To participate in the reformulation of Bluepharma's pharmacovigilance system, according to new pharmacovigilance obligations
- To prepare PSURs to the CA
- To participate in the preparation of RMPs
- To perform bibliographic search
- To understand and participate in individual case safety report (ICSR) collection, processing, assessment and reporting to CA
- To participate in the submission throughout EV Database of Bluepharma's medicinal products-related information
- To get acquainted with the Scientific Service structure
- To participate in Scientific Service activities'
- To get acquainted to the CTD structure as well as to the specificities of each module of the document
- To participate in exportation-related activities:
    - To identify the regulatory requirements for the registration of medicinal products in 3rd world countries as Mozambique and Cape Verde

- To elaborate/prepare and submit the specific documentation (product dossier and support material) for the registration of medicinal products in Cape Verde and Mozambique

Soft skills

- To contact with the working environment in a pharmaceutical company
- To develop skills of different types, such as organisational skills, time management, problem solving, responsibility sense, critical thinking, accuracy and attention to details
- To improve communication skill (verbal and written)

2. On-the-Job Training

This chapter intends to describe all the activities, tasks developed, and learning outcomes acquired during my curricular internship at Bluepharma.

For that, this chapter is organised in two sections:

- Multidisciplinary experience in which is described the training sessions attended. Some of them were mandatory for all collaborators and others were essential to understand the life cycle of a generic medicinal product and to perform the tasks and activities assigned during my internship.
- Specific experience in which is described my experience in the Regulatory Affairs and Pharmacovigilance department and the tasks and activities developed.

2.1. Multidisciplinary Experience

During my internship at Bluepharma, I attended different types of training sessions: ones that were mandatory for all collaborators, internal training sessions to acquire knowledge concerning different departments that closely interact with the Regulatory Affairs and Pharmacovigilance department and specific training sessions that allowed me to develop the different tasks and activities during my internship (Figure 4).

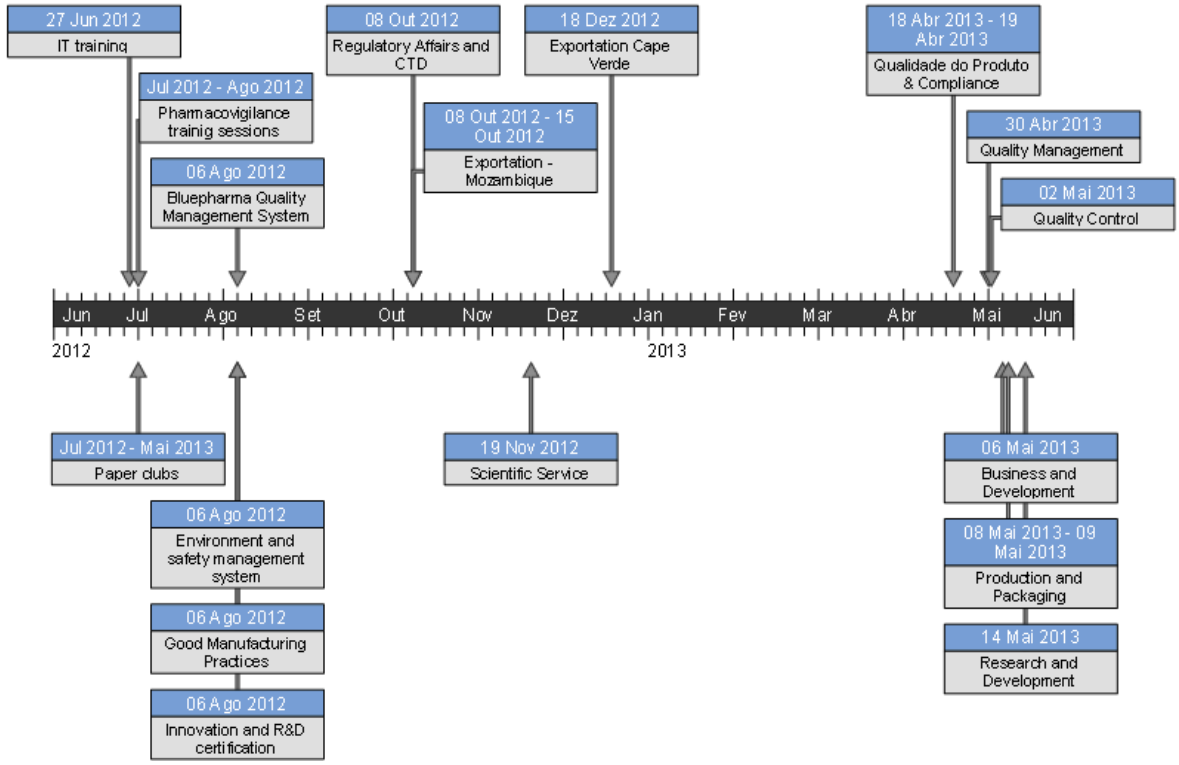

Figure 4 – Summary of training sessions attended during the internship period

Bluepharma is a certified company and consequently the integration of new collaborators comply with certain requirements namely training/information sessions concerning the main rules and principles of different areas of the company.

Consequently, when I started my curricular internship, I needed to acquired knowledge in general areas that were transversal to all company departments. This was done through self-reading of the company's quality manual and internal Standard Operating Procedures (SOPs) and training sessions.

I attended general internal training sessions concerning the following issues (Figure 4):

- Bluepharma Quality Management System
- Innovation and R&D certification
- Environment and safety management system
- GMPs
- Information technology services
- CTD contents and regulatory requirements

Aspects addressed in the several training sessions included Bluepharma's certifications, GMPs, CTD modules, type of authorisation procedures and regulatory requirements. Training on critical/relevant information technology internal SOPs and policies were also part of the general internal training sessions.

Those training sessions were very useful to refresh some concepts learned in my academic journey, such as quality systems, on CTD and on MA procedures as well as to acquire new concepts. During some of the sessions it was highlighted the importance of GMP and national and international regulations and their compliance in all the departments of the company.

Over the time, I also attended some additional brief formative sessions, named "paper clubs", which addressed different knowledge areas.

In order to understand how the company departments interact with each other, and to understand the company's dynamic and how the several departments work by themselves, I visited and had training sessions, according to a predefined schedule (Figure 4), in several departments such as R&D, Business and Development, Production and Packaging, Quality Control, Product Quality & Compliance and Quality Management departments.

2.1.1. Research & Development

In May, I followed the activities developed in the R&D department for a day. The objective of this observational training was to learn the basic principles of the pharmaceutical development process and how projects result in new products.

The R&D laboratory of Bluepharma is responsible for developing investigational projects, being responsible for the different stages of the development of products, namely

development of pharmaceutical formulations, development and validation of analytical methods, stability studies, manufacturing process development and up-scaling.

The development of generic medicinal products have different stages as it is described below:

1. Selection of the product;
2. Compilation of all possible information concerning the product, such as its description, pharmaceutical form, packaging material, sales of the innovator medicinal product, expected sales for the generic medicinal product, special manufacturing requirements, manufacturing site, intended batch size, and other relevant information;
3. Formulation development

    3.1. Characterisation of the innovator medicinal product and its API in order to select an appropriate formulation and the adequate manufacturing process;

    3.2. Characterisation of the drug product, namely in what concerns to the appearance, average weight, water content, hardness, disintegration, dissolution, content and related substances;

    3.3. Characterisation of the packaging material;

    3.4. Physicochemical characterisation of the API;

    3.5. Formulation development, focused on having similar dissolution profiles, as well as, impurity profiles, between the innovator reference product and generic medicinal product;

    3.6. Characterisation of the mixture (water content and homogeneity of the mixture) and the finished product (appearance, average weight, uniformity of mass, hardness, disintegration and dissolution);

4. Development and validation of analytical methods

In this phase, it is intended to develop and validate analytical methodologies that will be used to evaluate the API and finished product, as well as, any relevant intermediate product (i.e.: mixture or granules). The validation of a method allows to demonstrate that it is suitable for its intended purpose.

5. Laboratory batches

Laboratorial batches, which have a very small size, are produced, at early development laboratory stage, in order to assess and define critical product characteristics and consequently to select the appropriate manufacturing process.

6. Pilot-batches production

Pilot-batches are manufactured (in representative equipment) and controlled according to the data obtained in the steps above. For oral solid dosage forms, the pilot-batch size should corresponds to at least 100 000 units or at least 10% of the future industrial scale batch, whichever is greater. The pilot-batches are produced, packaged, and submitted to the ICH stability programme.

These batches will be used to feasibility studies, validation of the manufacturing process, up-scaling studies, stability studies and bioavailability-bioequivalence studies. The information obtained will be used in industrial batches manufacturing.

7. Stability studies

Stability studies are conducted to assess how the physicochemical stability of the product varies with time under the influence of different storage conditions (temperature, humidity and light) and to establish/propose a shelf-life for the medicinal product and recommend storage conditions, if needed [28]. Bluepharma follows the ICH guidelines.

The world is divided in four different climatic zones (I, II, III, IV). According to the climatic zone, the stability studies have different storage conditions and duration [29].

This day in R&D department, revealed a great opportunity to observe some processes used during the development of a product such as wet granulation, drying process and compression in laboratory scale. Since I have a degree in Biomedical Science, I have a limited knowledge in this area. I considered this day very helpful because I understood how a product “is born”. I got the opportunity to observe and participate in several processes that allowed me to comprehend many concepts that I had dealt with in many of my tasks in the Regulatory Affairs and Pharmacovigilance department, where the work relied on the product after being commercialised.

2.1.2. Business and Development

In May, I had a training session in the Business and Development department. Several themes were addressed namely: activities performed in this department, markets in which Bluepharma is present, intellectual property, pricing and reimbursement and the concerning legislation.

2.1.3. Production and Packaging

In May, I had the chance to accompany the activities conducted on the production and packaging department for two days. All the manufacturing processes have a manufacturing procedure that describe all the stages to be followed in the manufacturing process which are listed in the manufacturing protocol/record that is filled-in during the stages of the process.

To initiate the manufacturing process, the informatics system (SAP) generate a manufacturing order concerning to a specific batch. During the manufacturing process, the manufacturing protocol/record is filled-in and attached with all the relevant information, such as weigh registries, in-process controls (IPCs), and relevant manufacturing times (process duration and process ending times); at the end, all the information is compiled and verified, and it is performed yield calculation.

I had the opportunity to accompany different processes that are performed in this department:

1. Weighing

   Weighing is the start line. All raw materials (API) and excipients are weighed, after being entered in the SAP's system. This process is performed during several stages of the production of a medicinal product; mixtures before compression, or encapsulation, semi-finished product before packaging or bulk product for sale. Weighing is performed in suitable rooms and the operators must use personal protective equipment is accordance with the safety sheets of the product that will be handled.

2. Granulation

   – Wet granulation

   Granulation is performed in order to improve the characteristics of the mixture of the API, i.e., increase of the particle size, improvement of the compression process and flow properties, improvement of the content uniformity and/or increase of the solubility of the API.

   This process has different stages such as the preparation of the granulation solution/suspension, the granulation itself (mixture of the solids to be granulated with granulation solution/suspension), final sieving of the wet granulated mass and the drying process of the obtained granules.

   – Dry granulation

   When the raw material characteristics do not allow a wet granulation process, other type of granulation, named dry granulation, may be used.

   This type of granulation is a manufacturing process used to modify the pharmacotechnical properties of a product in order to facilitate the process of compression or encapsulation. In this process, there is the aggregation of particles by compaction (e.g.: roller compaction) which are then milled or sieved to the desired size.

3. Compression

   The tablets are obtained by compression, which may be a direct powder mixture compression or granulate compression. Bluepharma has different compression machines, which are fed vertically in order to prevent contaminations and product loss.

   The compressor has a combined unit constituted by a deduster, which makes the dedusting of the surface of the tablets and a metal detector that detects metal particles that tablets may contain.

4. Coating

   In some cases, the tablets are subjected to a coating process in order to cover unpleasant tastes and odours, facilitating swallowing, improving product stability and/or modifying the release profile or for aesthetical reasons.

This process takes place in an automated equipment and consists on the pulverisation of the tablets with a coating agent suspension and subsequent drying.

5. In-process control

   IPCs are conducted in regular intervals of time, during all the stages of the manufacturing process, in order to ensure the quality control and the process control.

   Several parameters may be monitored taking into account the product that is being manufactured and the related manufacturing process. Examples of IPCs include appearance, average weight, disintegration, length, hardness, friability and in closure system (capsules case).

6. Packaging

   Bluepharma is responsible for the packaging of some products derived from the production as well as products acquired in bulk; the packaging is performed not only for Bluepharma Genéricos but also for other clients.

   There is a Packaging Protocol for each product, and as in production, the packaging process may only begin once the Packaging Order is processed by the informatics system (SAP). The materials are informatically requested with the Packaging Order generation and are sent to the packaging sector, as soon as approved by the Quality Control.

   All the instructions are detailed in the packaging procedure and during the process, the line collaborators register in the packaging protocol relevant information. All the information concerning a batch is compiled and attached, being sent to the Product Quality & Compliance and Quality Control.

Accompanying these processes was an enriching experience since I had the opportunity to acquire theoretical competences concerning medicinal products' manufacturing and packaging that will be useful to develop my future work.

2.1.4. Quality Control

In May, I followed some of the activities performed in the Quality Control department for one day. This department is responsible for all the quality control activities that are set out

in the analytical protocols and that are required to ensure the medicinal products compliance with the GMP and applicable legislation.

All raw materials, packaging materials, intermediate products, bulk products and finished product are subjected to a sampling process in order to verify the product characteristics and confirm its compliance with applicable the specifications. Microbiologic and physicochemical tests are performed and the samples are stored. In accordance with the results, appropriate measures are taken.

2.1.5. Product Quality & Compliance

In April, I had a training session in the Product Quality & Compliance department for two days.

In that department, I had the opportunity to understand how the process of product release is performed. A brief overview of the process accompanied is provided below.

Product release

All the products produced at or for Bluepharma (bulk or finished product), to be release for selling or for supplying, must have a release authorisation that is a responsibility of the Qualified Person.

A certificate of release concerning the product for sale or a Certificate of Product Compliance (for bulk products) is emitted to authorise the effective release of the product to the client/market.

The Product Quality & Compliance department receives and verifies all the documentation concerning the production and/or packaging and quality control of the product's batch; the internal approval of all its components is performed by the Quality Control. The emission of the compliance certificate and the release of all products is a responsibility of the Qualified Person.

The last step of this process is to send the documentation concerning the product's approval/release to the client according to the technical agreement signed between Bluepharma and the client.

I also had the chance to attend a meeting to discuss the preparation of a manufacturing procedure and the respective manufacturing protocol.

2.1.6. Quality Management

Bluepharma has implemented a Quality, Environmental, Health and Safety Management System. A management system is what the organisation has in place to manage their processes or activities in order to assure, monitor and promote that the products/services efficiently achieve their objectives [30].

Bluepharma's quality system is implemented throughout the product lifecycle enhancing an innovator and continual improvement and strengthening the link between pharmaceutical development and manufacturing activities.

In 2003, Bluepharma obtained a combined certification in Quality, Environment, Safety and Occupational Heath supported by International Organization for Standardization (ISO) Norms 9001, ISO 14001 and Occupational Health and Safety Advisory Services 18001 and Regulation No 1221/2009; recently obtained the certification in Portuguese Norms of Research, Development and Innovation.

I also had the possibility to observe other activities developed by the department such as change control processes, supplier management process, SAP management and customer satisfaction surveys analysis.

After these training sessions, I concluded that it was a very useful and fruitful experience. I had the possibility to be in touch with different areas, and acquire different skills/competences concerning the medicinal product life cycle, since the moment that a new project is planned to its preparation for the market phase. The purposes of these training sessions were to know the activities performed in each department and be familiarised with the processes and support documentation used.

2.2. Specific Experience

This section describes the main activities performed in the Regulatory Affairs and Pharmacovigilance department. The main activities developed during my internship were related to the pharmacovigilance area and consequently, this section is focused on this field. However, I also accompanied scientific service and exportation activities, and that are also included.

2.2.1. Pharmacovigilance

2.2.1.1. Pharmacovigilance System Master File

Overall requirements

The new pharmacovigilance legislation introduced the concept of the Pharmacovigilance System Master File (PSMF) [23]. PSMF details the pharmacovigilance system used by a MAH to cover one or more authorised medicinal products. It contains summarised information and key documentation that cover all the pharmacovigilance activities aspects [31].

For centralised procedures, after 2 July 2012, as well as for National submissions, after 21 July 2012, all new MA, must present a PSMF. All medicinal products approved before these dates have a deadline to have available this document (transitional period until July 2015).

PSMF does not have an available template. However, the Commission Implementing Regulation and GVP Module II describe its content and structure.

Working experience

During my internship period, I had the chance to collaborate in the preparation and implementation process of the company's PSMF. The pharmacovigilance service collaborators jointly prepared the PSMF. For that, we had to analyse the EU legal requirements and relevant GVPs in order to create the company's PSMF [23, 32]. Finally,

we compiled the information required and wrote the different sections of the PSMF, which are described below: [10, 23]:

- Qualified person responsible for pharmacovigilance (EU-QPPV) information section
    - Responsibilities of the EU-QPPV (that detains the responsibility over the pharmacovigilance system)
    - Summary of the curriculum vitae of the EU-QPPV (including a proof of registration in the EV database)
    - Contact details of the EU-QPPV
    - Nomination of the EU-QPPV deputy
- The organisational structure of the MAH
- The computerised systems and databases used
- Pharmacovigilance processes
- The quality system for the performance of pharmacovigilance activities

Besides the core of the PSMF, there is a specific section for annexes, which was also prepared. The information presented in this section is very detailed and in continuous updating since we are working in a dynamic system.
Once the PSMF was prepared, it was registered in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD). An acknowledgement was sent by the system (via EV) to the MAH, which confirmed the success of the registration. This registration, allowed the PSMF to have a code number associated to where it was located. This is the information required by the authorities. However, the authorities can request the PSMF itself and the MAH has a period of seven days to make it accessible to them.

When I started my internship, the pharmacovigilance service was planning the preparation and implementation of the PSMF as well as the summary of the pharmacovigilance system required for MA applications. This was a very important and challenging activity since it allowed me be involved in the implementation of a new system and to acquire knowledge in the new legislation on pharmacovigilance.

2.2.1.2. Pharmacovigilance Quality System

Overall requirements

In accordance with the new pharmacovigilance legislation, the MAH has the obligation to have in place adequate and effective quality systems for the performance of their pharmacovigilance activities. The Commission Implementing Regulation No 520/2012 defines the minimum requirements of the quality systems which should cover company organisational structure, responsibilities, procedures, processes and appropriate human resources, management of resources, compliance management and record management [32].

Since the company's procedures in place before the new legislation on pharmacovigilance were not enough to comply with the new requirements, the company's processes and SOPs were reviewed and new ones were created.

Working experience

I had the opportunity to participate in the planning, redesign and in the restructuration process of the pharmacovigilance system implemented by the company.

First, the pharmacovigilance service collaborators' performed a meeting in order to discuss the new requirements of the pharmacovigilance legislation and to define new processes and procedures to be implemented and the way they would be executed, in which I contributed giving some ideas.

After designing and planning the new pharmacovigilance system, the existing SOPs were reviewed and new ones were created as well as their respective related-forms. I was able to contribute and participate in this task.

The main areas covered by the prepared processes and procedures were the following [32]:

- Risk minimisation system(s) and monitoring of the outcome of risk minimisation measures;
- PSUR scheduling, preparation and submission;
- ADR collection, collation, validation, follow-up assessment and reporting to the CA;

- Signal detection and analysis;
- Communication of safety concerns to the CA, healthcare professionals and consumers;
- Safety issues.

This task revealed itself very challenging since several areas were involved and each one had different specificities. These activities helped me to understand how different SOPs are prepared and implemented in a pharmaceutical company with a certified quality system. In addition, it was helpful since it allowed me to be in touch with all the pharmacovigilance activities and understand how the pharmacovigilance activities would be performed after the system is implemented. I also gained experience in SOPs writing, which is a highly valued skill in this area.

The application of the new legislation is not a static process and requires constant adjustments. Hence, the companies had to be attentive to sudden modifications, as it has been happening until now, for example, in the case of the publication of lists for the submission of PSURs or RMP and PSUR templates', which can easily lead to non-compliance, if not taken into account.

Regarding this subject, I had an important role and responsibility on the monitoring, on a weekly-based, the most relevant regulatory bodies' web sites and publications, such as EMA, INFARMED, I.P. and Heads of Medicines Agencies. The objective was to obtain the most updated information concerning all the pharmacovigilance issues and subsequently analyse and communicate the impact, if applicable, of such modifications on the implemented pharmacovigilance system.

2.2.1.3. Individual Case Safety Reports

The new pharmacovigilance legislation introduced a new definition of ADR. According to Directive 2010/84/EU, an ADR is defined as "a response to a medicinal product which is noxious and unintended." "Response to a medicinal product" in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility [23]. This includes adverse reactions which arise from the use of a medicinal product within and outside of the terms of the MA, including overdose, off-label use, misuse, abuse and medication errors and also occupational exposure [23]

In accordance with the Directive 2001/83/EC as amended, ADR may be classified concerning the seriousness. An ADR is serious when results in death, life-threatening, requires patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or in a congenital anomaly/birth defect [23].

Processing ICSRs

During my internship, I collaborated in the processing of ICSRs. This process encompasses four main stages: collection, validation, assessment, and report.

1. Collection

ADR can arise from unsolicited or solicited reports. Unsolicited reports are divided in spontaneous reports, literature reports and reports from other sources. Solicited reports arise from organised data collection systems as clinical trials, non-interventional studies, registries, patient or disease management programmes, surveys of patients or healthcare providers, and others [31].

A spontaneous report is an unsolicited communication that describes one or more suspected ADR(s) in a patient who takes one or more medicinal product. This type of report is performed by a health care professionals or a consumer to the CA, MA or other organisation as the Regional Pharmacovigilance Centre [33].

Suspect adverse reactions from health professional and consumers

According to my experience at Bluepharma, health care professionals and consumers can report a suspect ADR by different channels of communication such as the company's website, telephone, email, fax, the company sales representatives and others.
The information is processed taking always into account that the clock starts when someone in the company becomes aware of the suspect ADR and that depending on the seriousness of suspect ADR the reporting deadlines are different. Therefore, the information received is analysed and always recorded in internal databases.

During my internship, I had to process one case. Bluepharma was contacted by a health care professional and I had the chance to take the call and ask all the questions in order to obtain all the necessary information concerning the suspected ADR to process the case. After that, I also collaborated in the registration of the received information by filling-in the respective internal forms and by inserting the data in the databases.

One of the responsibilities that was assigned to me was to maintain the ICSR databases (according to the information given to me).

Suspect adverse reactions from literature search

Scientific and medical literature provides important information concerning the safety and efficacy of medicinal products, allowing companies to monitor the benefit-risk profile of their medicinal products [33].

According to their obligations, the pharmaceutical companies conduct a systematic literature review through widely used reference databases at least once a week for all active substances of their medicinal products with MA, irrespectively of commercial status. The literature search starts after the MA is granted and is performed during the product life cycle [33].

During all my internship period, I assured the fulfilment of this pharmacovigilance activity. Thereby, I had to perform a systematic literature review, on a weekly basis, in order to comply with the regulatory requirements.

Widely reference databases were used to perform the search, which was performed according to previously defined search criteria for all active substances of the company's medicinal products. First, I received the articles, read their abstracts, and verified the information.

Whenever a publication presented a case in which it was identified that the suspected medicinal product was an active substance of a Bluepharma medicinal product, an ICSR was created.

To be a valid case, the publication had to fulfil the minimum criteria for reporting (see next section). The weekly search was always documented for compliance purposes. After analysing the publication, my function in this regard was to insert all the relevant information in an appropriate database and archiving the relevant documentation.

2. Validation

The information received from the different sources needs to be verified in order to understand if it qualifies as a valid case.

Therefore, according to GVP – Module VI, I verified if the case was considered valid or not. To be considered a valid case, it had to fulfil the minimum criteria for reporting [33]:

- One or more identifiable reporter;
- One single identifiable patient characterised by initials, patient identification number, date of birth, age, age group or gender;
- One or more suspected substances/medicinal product;
- One or more suspected adverse reaction.

The information received can easy be incomplete and consequently, the reports need to be followed-up to obtain the detailed information required to analyse the case. There are two main types of follow-up: a follow-up to gather missing information or clarify misleading data; and a follow-up to complete or supplement a reported case, which is particularly important in cases as serious ADR or pregnancy exposure reports [33].

In those situations, a request is usually sent to the primary reporter by means of a telephone call or if it is not possible, on an e-mail.

Whenever a case report does not include the minimum criteria for reporting, even after the follow-up contact, the case is closed and only reported if additional information becomes available. Otherwise, if the case is valid, the next step is its evaluation.

3. Assessment

In accordance with the directive 2010/84/EU of 15 December 2012, the concept of ADR includes the existence of at least a reasonable possibility of a causal relationship between a medicinal product and the adverse event [23].

In order to evaluate the relationship between the medicinal product and the observed ADR, various causality assessment methods are available. This evaluation may be performed by establishing algorithms, Bayesians systems or by making an evaluation after gathering all the information obtained from the reporter, the safety documents, the physician's report

and all known safety information about the product in question. [34]. The following criteria are taken into account and analysed [26]:

- Time relationship to medicinal product intake
- Response to withdrawal plausible
- Rechallenge data
- ADR profile
    - Clinical and laboratorial findings
    - Seriousness and severity
    - Possible mechanism of action
    - Causality relationship
    - Predisposed factors
    - Reversibility and sequels
- Pharmacological or phenomenological plausibility
- Complementary investigational data
- Concomitant diseases
- Concomitant medicinal products

The reference document used to evaluate the relevance of the information related to the ADRs received and the determination of the benefit-risk balance of a medicinal product is the suspect medicinal product's summary of product characteristics (SmPC) available on the country where the suspect ADR occurred.

One of my duties on this regard was to analyse the suspect medicinal product's SmPC, in order to understand the expectedness of the ADR. An ADR may be classified as expected or unexpected: i.e., an expected ADR is described in the SmPC in terms of nature, severity and outcome. In the case of an unexpected ADR, none of this items are stated in the SmPC [23].

Other of my roles was to verify if the description of the reported suspected adverse reaction was in accordance with the medical dictionary for regulatory activities (MedDRA) terminology, which was created for standardising the terminology used in regulatory information for medicinal products of human use.

During my internship, I accompanied the assessment of ICSRs by the pharmacovigilance service's collaborators and medical advisor. At the end, it was decided whether a suspect adverse reaction is reported to the CA.

4. Report of ICSR

In accordance with the new pharmacovigilance legislation, the MAH and the Member State should communicate ADR electronically only through the EV database. The objective is to simplify the reporting of ADR and make available through a pharmacovigilance database the safety information concerning medicinal products on the EU [23, 33].

The new legislation also introduced changes in the timeframe for the reporting of ADR, which currently are the following:

- All serious ADR that occurred within the EU should be reported within 15 days;
- All non-serious ADR occurred within the EU should be reported within 90 days (during the transitional period, only if required by MS);
- All serious ADR occurred outside the EU should be reported within 15 days.

EV database will allow the submission of ICSRs, but it is not yet completely functional. Consequently, in accordance with Directive 2010/84/EU, until the EMA can ensure the functionality of the EV database, there are being applied interim arrangements [23].

EMA published a document entitled "Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to MAH during the interim period" which defines the requirements of ICSR reporting depending on the MA procedure, origin, ADR type and destination MS.

In accordance with the Decree-Law No 176/2006 of 30 August, amended by the Decree-Law No 20/2013 of 14 February, and until the EV database is concluded, INFARMED, I.P. does not require the notification of non-serious ADR (only when expressly solicited). However, the MAH is responsible for analysing and recording all these cases and present them whenever solicited by the CA.

Until the electronic submission via EV is completely functional, the transmission of ICSRs is performed by filling-in the CIOMS form I or after a process of several transmission tests

and procedures with INFARMED, I.P. is validated, the transmission of only serious ADR can be reported through the EV platform.

CIOMS form I

This document was prepared by Council for International Organizations of Medical Sciences (CIOMS), which is an organisation established in 1949 by a partnership between WHO and United Nations Educational, Scientific and Cultural Organization. This group develop guidelines in the pharmacovigilance area, including the CIOMS form I, which is a reporting form for ADR internationally recognised.

Consequently, I also had to fill-in CIOMS forms I with the ICSRs information in order to send them to INFARMED, I.P. The CIOMS form I is filled-in with all the available information concerning the case including information related to the patient, primary source, suspect ADR and the suspect medicinal product. It is desirable that all the fields of the form are completed, but frequently not all the information is available, consequently it should only be ensured (in validation stage) that the minimum criteria for report are present. Finally, every time a suspect ADR had to be reported to INFARMED I.P., the CIOMS form I was sent to the Directorate of Medicines Risk Management by email.

EudraVigilance database: Electronic transmission of ICSRs

Currently, the reporting of serious ADR to INFARMED, I.P. is performed by the EV database since this communication channel was approved by the National CA. Consequently, I had the opportunity to learn the functionalities of the EV database, how it works, and how a case can be reported to INFARMED, I.P.

The images outputs and cases used in this section to describe the functionalities and rules of the EV database are fictitious, and are intended for demonstration purposes only.

EV database is the “European data-processing network and database management system which allows the reporting and evaluation of Adverse Events and ADR during clinical investigation and post-authorisation phase of medicinal products in the European Economic Area”. The creation of the EV database aims to improve the capability of transmission of safety information between pharmaceutical companies and the European CA [35].

The access to EV platform is by the EV web application, called EVWEB, which is a tool designed for electronic transmission of ICSRs to the EV database through the internet [35].

During my internship, I accompanied and, in some cases participated in reporting of ADR through the EV database, by collecting and gathering all the information to be submitted in the platform.

First, for reporting an ADR, it is needed to access to the EV web site [36] and then choose the option "Production" on the right side menu on the top of the page, as presented in Figure 5.

Figure 5 – EV database web site output, available on the Eudravigilance web site [36]

After left click on "Production," a new window opens and it is needed to enter the login user and the password to have access to the restricted area. Then, a new window appears and the option EVWEB should be selected, as presented in Figure 6. Subsequently, the EVWEB application will open in a new browser window.

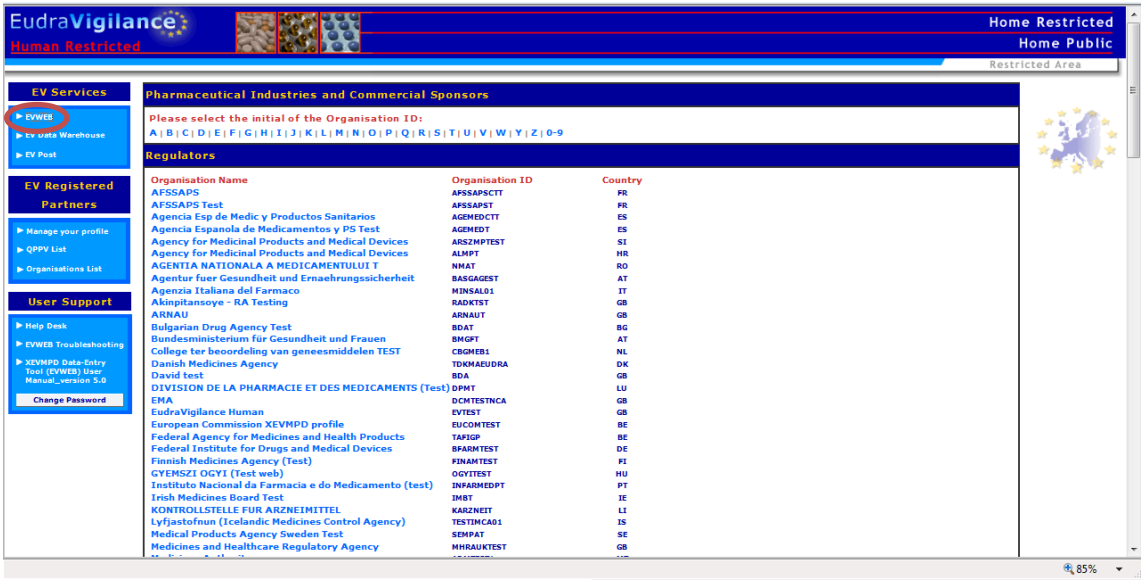

Figure 6 – EV Services menu, available on the Eudravigilance web site [36]

The new browser window has a main menu located at the top of the screen and contains the default buttons and the dynamic buttons (Figure 7).

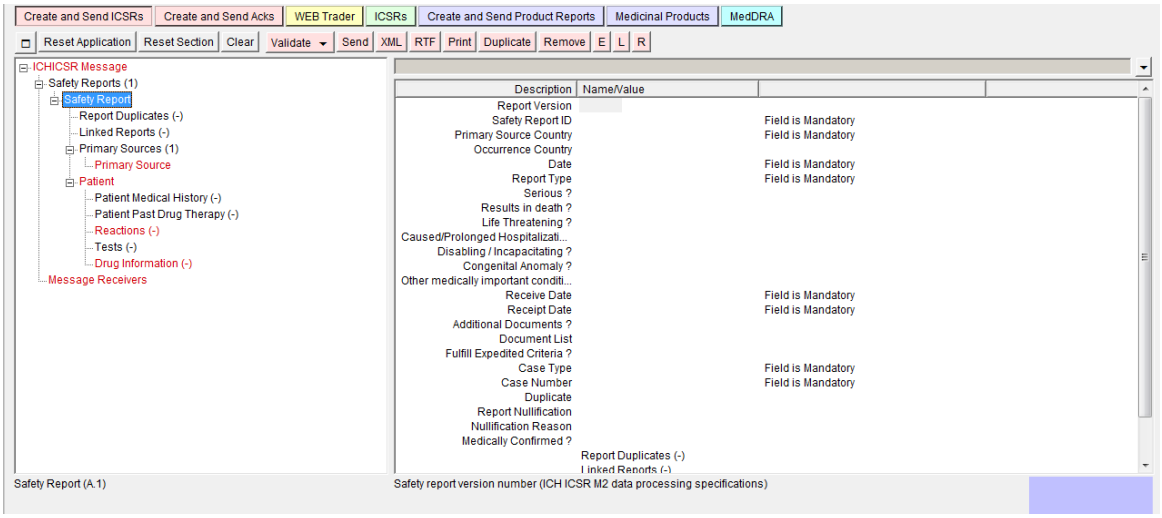

Figure 7 – Output after choose the option "send ICSRs", available on the Eudravigilance web site [36]

The buttons enable to perform different activities:

- Create and send ICSRs (button "Send ICSRs");
- Create and send acknowledgments (button "Send Acks");
- Access to the inbox and outbox folders as also to import messages saved on the computer (button "WEB Trader");

- Browse and perform searches on the ICSRs that were submitted by the MAH (button "ICSRs");
- Create and send XEVMPD Product Report Message (button "Send Products");
- Verify the XEVMPD (button "Products");
- Browse and perform searches on MedDra (button "MedDra").

Whenever there is an ICSR to report, the option "Send ICSRs" is chosen and a tree view appears on the left side of the application, below to the main navigation menu, as highlighted in Figure 7. Generally, the elements in the tree view can be expanded allowing the introduction of more information.

The fields that appear on the right side are completed, but not all the fields are mandatory since in a large number of cases, not all information is available. Each field have specificities that are explained in ICH E2B (R2) guideline.

The information provided, in the EV database, is related to, but not only:

- Safety report: information concerning the safety report identification, date of transmission, type of report, date when the report was received by primary source, seriousness of the ADR and other information
- Primary source, i.e., the person who reports the facts: title, name, organisation, country; in case of literature search the literature reference should be included and in case of a study, the details on trial type should also be provided
- Patient characteristics: patient initials, birth date, age, investigational number (in case of a clinical trial), patient age group, patient sex;
    - Patient medical history;
    - Patient past drug therapy;
    - Reaction(s)/Event(s): reaction reported by primary source, MedDra code for the reaction, start date, end date, duration, outcome;
    - Test/procedure results relevant for the investigation;
    - Drug(s) information: including suspect drugs and concomitant medications and also drugs thought to have an interaction: Proprietary Medicinal Product Name, authorisation status, authorisation country, MAH, dose, route of administration, indication, date of start of drug, last administration

date, action taken (drug withdrawn, drug reduced, drug increased, dose not changed, unknown, not applicable;

- Patient death (if applicable): death date and autopsy including patient cause of death;
- Parent-child report (if applicable): parent information.

Once all the fields, for which there is information available, are completed, it is selected the message receiver, which for the medicinal products authorised in Portugal, is the INFARMED, I.P. After selecting INFARMED, I.P. it is necessary to validate the case in the button "Validate" on the top of the screen and then, if no errors are detected a XML (Extensible Mark-up Language) and a RTF (Rich Text Format) file copy are saved and subsequently the safety case is submitted.

The electronic transmission is based on XML files, format in which the safety message is sent and contains one or several ICSRs. The advantage of saving a copy in that format is that it is the only format accepted by the database and the only way to import a file from the computer to the EV database, in case of follow-up.

After sending the message, there is a confirmation of the reception of the information called acknowledgment (ACK). The receiver processes the safety message and then, sends an ACK message informing whether the report was accepted or not and in the negative cases the reason(s) why.

There are three transmission ACK codes:

- ACK 01 – When the ICSR does not contain any errors and consequently the safety reports are loaded;
- ACK 02 – When the ICSR contain errors and consequently not all safety reports are loaded;
- ACK 03 – When no data can be extracted from the safety message resulting in a message or system error.

Accompanying the activities related to this platform, it allowed me to observe how the EV database works and understand their functionalities. It was a very important task, because this is a new tool used in Europe for pharmacovigilance purposes and all the companies need to have trained collaborators in that field, in order to comply with the regulatory

requirements. The EV database is a complex data processing and management system that requires training for its use. I had the chance to learn it with the company's EU-QPPV, who has the certificates that give her the competencies to work with the platform.

2.2.1.4. Periodic Safety Update Reports

Overall requirements

Periodic Safety Update Report (PSUR) summarises and gathers data and information regarding the safety of a medicinal product during its lifecycle. This report is then, evaluated by the authorities that analyse the ratio of benefit/risk of the medicinal product in question. All potential risks are evaluated in order to protect public health [37].

PSURs are submitted with a determined frequency and consequently the information contained covers a determined period. The cut-off date of the data included in the PSUR is designated as data lock point (DLP) [37].

The submission of the frequency of submission and DLP are laid down as a condition on the MA or it is determined in the list of Union reference dates and frequency of submission of periodic safety update reports (EURD) [34].

With the new pharmacovigilance legislation, the EMA created the EURD list, which is made public by EMA and updated monthly. This list includes active substances and combinations of active substances contained in medicinal products authorised in the EU. It was compiled in order to facilitate the harmonisation of the frequency submission of PSURs and DLPs for the medicinal products authorised in EU [37]. The first EURD list was published on October the 1st 2012 and came into force on April the 1st 2013 [34].

Before the new legislation, it was an option to the MAH to subscribe the PSUR Work Sharing and Synchronisation Project. This project included the publication of two lists: the PSUR Work Sharing list and the PSUR Synchronisation list. However, the accession to this project was voluntary as its lists did not included all active substances and combination of active substances present in the medicinal products authorised in EU [37].

The new pharmacovigilance legislation introduced another change concerning PSURs. These reports are not always required for generic medicines, medicines whose use is "well-established", homoeopathic medicines and traditional herbal medicines. Depending on the

active substance, the EURD list demands or not the submission of PSURs in the case of this type of medicines [37].

Working experience

During my internship, I collaborated in PSURs preparation and submission to INFARMED, I.P. In order to accomplish this activity I had to collect relevant information and write different sections of the PSUR. I had the opportunity to follow the submission of PSURs to the authorities.

First, I had to collect the information used to prepare a PSUR, which is provided by efficacy, effectiveness and safety sources, such as [37]:

- Internal information related to the volume of sales of a medicinal product during the timeframe of the report, reference safety information (SmPC), and pharmaceutical/medical sales representative suspect of ADR notifications, literature research;
- External information is related to spontaneous reports from health care professionals and consumers, regulatory authorities and safety data exchange agreements with external partners.

I also had to research and collect information concerning the characteristics of the medicinal product (as chemical class, mechanism of action, pharmacotherapeutic group, ATC code and others) and regulatory authorities' information (MAH, MA date, MA number(s), international bird date, EURD, and others.

Then, I began writing the different sections of the PSUR.

According to the Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012, the PSUR template presents the following sections:

- Part I: Title page including signature4
- Part II: Executive Summary
- Part III: Table of Contents

1. Introduction
2. Worldwide MA status

3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns
6. Data in summary tabulations
7. Summaries of significant findings from clinical trials during the reporting interval
8. Findings from non-interventional studies
9. Information from other clinical trials and sources
10. Non-clinical Data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information
15. Overview of signals: new, on-going, or closed
16. Signal and risk evaluation
17. Benefit evaluation
18. Integrated benefit-risk analysis for authorised indications
19. Conclusions and actions
20. Appendices to the PSUR

National CA and EMA have different requirements for PSUR submission [38]. For national procedures, INFARMED, I.P. requires that the PSUR is sent in a registered correspondence [38].

Consequently, the next step consisted on preparing the registered correspondence, addressed to INFARMED, I.P., which contained a signed cover letter (required by the National CA) and one PDF copy of the PSUR in electronic format (CD-ROM).

Furthermore, any CD-ROM sent to INFARMED, I.P. must contain the appropriate identification of the product in question as the product's name, dosage, pharmaceutical form, MAH and DLP.

I also prepared the identification of the CDs, using an optical disc recording technology, which allows direct disc labelling. As a result, all the information considered necessary for

the identification of CD-ROM was directly printed on each CD-ROM by the use of specific software.

During my internship, I acquired the capability to perform this task in an independent way, performing the management of the schedule of PSURs submission according to the DLP of each product and subsequently the preparation for the submission of the report.

The preparation of PSURs was very useful since I understood how to acquire the baseline information for its preparation, how the benefit-risk analysis of a product is conducted and also, how to manage my time in order to comply with the deadlines. All the processes are extremely meticulous and rigorous because medicinal products are manufactured for persons and their safety must always be ensured. Therefore, I learned to be more rigorous in all the process, even in the simple ones and to pay attention to all the details to try to minimise the errors, since they may always arise.

2.2.1.5. Risk Management Plan

The new legislation on pharmacovigilance introduced the requirement to submit RMPs for all the new MA applications [23, 24].

The MAH has to have in place a risk management system, i.e., "a set of pharmacovigilance activities and interventions design identify, characterise, prevent or minimise risks relating to medicinal products". All those activities should be assessed in terms of its effectiveness [39].

The preparation of a RMP of a generic medicinal product is based on the already available data of the innovator's product.

The RMP template is set out in the Commission implementing regulation (EU) No 520/2012 of 19 June 2012. The GVPs have also a module dedicated to this matter, where the risk minimisation principles are discussed and the format and content of a RMP are presented in order to harmonise and facilitate their preparation by the MAH and assessment by CA [32].

During my training period, I participated in the preparation of RMPs, which allowed me to be in touch with their structure and to understand how the information is collected. The

structure of a RMP consists in seven parts and some parts are subdivided in modules, the structure of a RMP is presented below [32]:

- Part I: Product(s) overview
- Part II: Safety specification
    - Module SI: Epidemiology of the indication(s) and target population(s)
    - Module SII: Non-clinical part of the safety specification
    - Module SIII: Clinical trial exposure
    - Module SIV: Populations not studied in clinical trials
    - Module SV: Post-authorisation experience
    - Module SVI: Additional EU requirements for the safety specification
    - Module SVII: Identified and potential risks
    - Module SVIII: Summary of the safety concerns
- Part III: Pharmacovigilance plan (including post-authorisation safety studies)
- Part IV: Plans for post-authorisation efficacy studies
- Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)
- Part VI: Summary of the risk management plan
- Part VII: Annexes

During my internship, I learned to prepare a RMP. I also understood, the difference between the requirements of a RMP for an innovator and the ones for a generic medicinal product.

2.2.1.6. EudraVigilance Medicinal Product Dictionary

Overall requirements

In accordance with the Regulation No 1235/2010 of the Council of 15 December 2010, the EMA is responsible for setup and maintain a list of all medicinal products for human use authorised in the EU. As a result, the MAH had to submit electronically to EMA, until 2 July 2012, information concerning all medicinal products of human use authorised in the EU through the XEVMPD.

Working experience

One of my tasks was to support the EU-QPPV to submit Bluepharma's medicinal products through the EV database.

My role was to search and gather all the information needed to complete the fields requested. I collected and organised information, in order to allow a faster electronic submission.

This information came from:

- Reference information, i.e. SmPC;
- Regulatory medicinal product information (such as MAH, MA numbers, MA date);
- Pharmacovigilance information.

Electronic submission of medicinal product information

To submit the medicinal products information we have to have access to the EV database according to the steps followed in the ICSR reporting; however, instead of choosing the option "Send ICSRs", in this case, it is chosen the button "Send Products", in order to open a window as presented in Figure 9.

The information is inserted in the fields that appear on the right side, but not all the fields are mandatory (Figure 8).

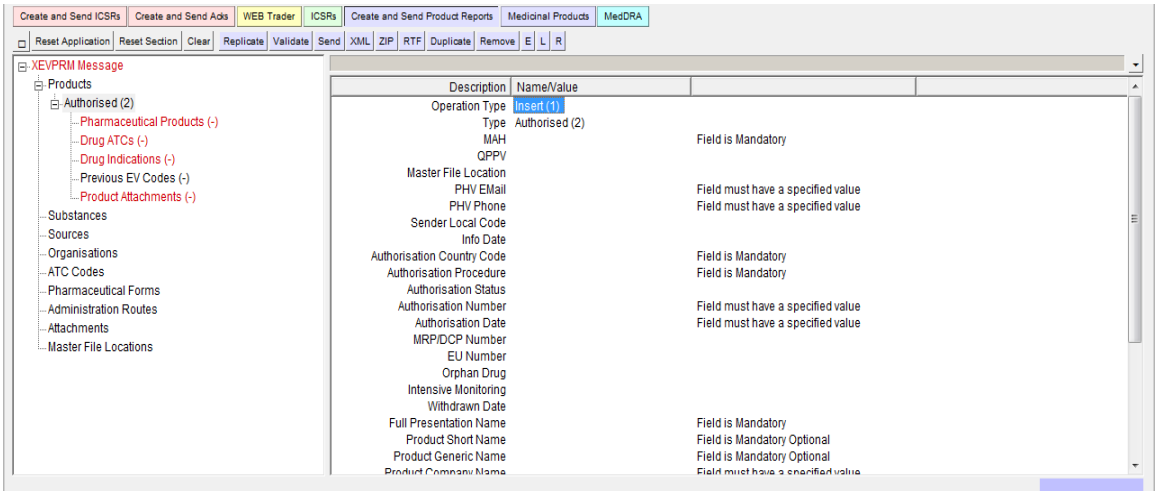

Figure 8 – Tree view after choose the button "Send Products", available on the Eudravigilance web site [36]

Once all the necessary information is entered, the button "Validate" on the top of the screen was chosen, in order to verify if all the mandatory information was introduced and the data that was entered. If no errors occur, the message is ready to be sent. A XML and a RTF file are saved on the computer and subsequently, the XEVPRM is sent by choosing the button "Send".

In the outbox, it is possible to check if the XEVPRM was sent and in which date. In the case of XEVPRM, an ACK is also received. The ACK process is the same as mentioned in the ICSR messages section.

Consequently, after receiving an ACK 01 (medicinal product successfully introduced on the database) it is recorded on the computer for compliance purposes.

In order to manage efficiently the information sent and received, a management file was created, which allowed registering and understanding the type of information sent and the day, the ACK received and in which date and if the information was successfully entered in the EV database.

Participating in these tasks allowed me to understand and observe how this new European tool works and presents itself, which is of extreme importance for a person that is working in the pharmacovigilance area. I was able to acquire knowledge concerning the company products that is always important when we belong to Regulatory Affairs and Pharmacovigilance department.

2.2.2. Scientific Service

2.2.2.1. Advertising of medicinal products

Overall requirements

The medicinal products advertising is regulated by the Decree-Law No 176/2006 of 30 August, amended by the Decree-Law No 20/2013 of 14 February, Deliberation 044/CD/2008 – Advertising Regulation and Ministerial Directive No. 157/2009 - National Council for Medicinal Products' Advertising.

In accordance with the Portuguese Decree-Law No 176/2006 of 30 August as amended, the medicinal products' advertising is considered to be any kind of information, prospecting or incentive with the object or the effect of promoting its prescription, distribution, sale, purchase or consumption under any of the circumstances set out in this decree-law [17].

Institutional advertising

Institutional advertising do not include specific reference to any medicinal product and only contains reference to the company. This type of advertisement is not considered medicinal product advertising, therefore, it is not subject to the same regulatory requirements [17].

Advertising among health care professionals

When a medicinal product advertising material is prepared for health care professionals, the following elements are included in the advertising peace, in a legible way [17, 40]:

- Name of the medicinal product;
- Essential information compatible with the SmPC, including qualitative and quantitative composition, pharmaceutical form, indications, posology, route of administration, contraindications, and undesirable effects. Other elements that may be included, if clinically relevant: special warnings and precautions for use and interaction with other medicinal products and other forms of interaction.
- Medicinal product's classification for dispensing purposes
- State's subsidies system.

In addition, the advertising to prescription-only medicines is restrict to health care professionals, which implicates that the advertising is performed by means that allow the exclusive access to health care professionals, namely congresses, symposiums or any other actions or events of scientific nature. The advertising can only be performed for medicines with a valid authorisation or registration in the national market [9].

General public advertising

Advertising to general public is only permitted for medicinal products not subject to medical prescription, once they do not contain substances defined as narcotic or

psychotropic or are subsidised by National Health Service. Advertising pieces for general public have at least the following elements: name of medicinal product, indispensable information for the rational use of the medicinal product, including therapeutic indications and special precautions; advice to the user to careful read the information included in the secondary packaging and PIL and, in case of doubt or symptoms persistence to contact the doctor or the pharmacist [17, 40].

Working experience

During my internship, I participated in the activities associated with institutional advertising and medicinal products advertising.

Medicinal product advertising

I had the opportunity to accompany the preparation of an advertisement piece and then participate in the process. My work consisted on preparing the essential information, based on the medicinal product's SmPC, to include in an advertising piece to health care professionals.

INFARMED, I.P. requires the submission of a descriptive memory of any medicinal product advertising piece throughout the medicinal products advertising management system (GPUB) available on the INFARMED, I.P. website within 10 days starting on the date of publication of the advertising piece or the date of publication of an advertising piece integrated on promotion campaigns or annual plans (Figure 9) [41].

I accompanied the notification process to INFARMED, I.P. through the GPUB system of some advertising pieces. For that, we accessed INFARMED, I.P. web site, and then chose the option GPUB [41]. The next steps followed were:

- Choose the option "Nova Notificação" on the left side of the screen as presented in Figure 9;
- Complete the fields concerning the advertising piece data presented in Figure 10;
- Choose the button "Criar notificação";
- On the left side of the screen there is a button that allows seeing/confirming the notification already sent.

Figure 9 – Notification form in GPUB, available on the INFARMED, I.P. [41]

The scientific service is responsible for the information regarding the company's medicinal products. The institutional and medicinal product advertising documentation is archived and maintained by a minimum period 5 years [17], consequently, I also had to archive hard and electronic copies of the notifications and support documentation, such as the material of medicinal product advertising.

2.2.2.2. Information request management

In accordance with the Decree-Law No 176/2006 of 30 August as amended, the companies have the obligation to have a Scientific Service responsible for providing information concerning the medicinal products for which the company holds a MA [17].

It was explained to me and I observed how the scientific service receives and manages the information requests. The main steps are described below:

1. Scientific service receives and registers all the information requests concerning Bluepharma medicinal products coming from consumers or health professionals and performs its adequately treatment and response according to whom presents the request.
2. When the request is received, it is registered taking into account the requester's identification, contacts, and description of the request and also the solicited response deadline.
3. The information is assessed in order to verify if there is a quality or safety issue. If not, the request is valid and a response is prepared and sent to the requester.

Accompanying and developing some of these tasks allowed me to gain experience in the advertising and information requests areas.

2.2.3. Exportation

2.2.3.1. Certificate of pharmaceutical product request

Overall requirements

When a company intends to export or register a medicinal product outside of the European Community, the importer country generally requires evidence of the MA and/or manufacturing status in the exporter country [42].

INFARMED, I.P. issues a Certificate of a pharmaceutical product (CPP) which complies with a WHO specific format. This certificate indicates whether the product meets statutory requirements providing details about the medicinal product, which may be licensed or unlicensed in Portugal. It can also be granted a certificate of a product without a MA. It is granted based on the Manufacturers Authorisation for exportation.

In the certificate there are provided details about the product and its production including medicinal product name, dosage form, active ingredients and excipients present in the medicinal product, commercialisation status (if applicable), MA information (if applicable), manufacturer and other information.

In order to INFARMED, I.P. issue a certificate, the applicant must send a CPP request form and pay the respective fee, that is different depending on the number of products and/or number of doses of the medicinal product and the number of original copies required [43].

Working experience

During my training, I participated in the process of requesting CPPs. For that, I had to fill in the CPP forms for several medicinal products and the respective payment guide, in coordination with the financial officer, in order to pay the charged fee.

There are specific rules for which is necessary to pay attention. INFARMED, I.P. made available specific rules for naming the documents that will be sent to them. The application form should be identified as FORM_COMS_medicine name_date, the payment guide should be named as GP_name of the company_date, in addition the proof of bank transfers is also sent and identified as TB_ company name_date [43].

After gathering all needed documents and payment, an email is sent with all the documents to certificado.medicamento@infarmed.pt [43].

2.2.3.2. Registration of medicines in Mozambique

Overall requirements

The registration of products in Mozambique is performed according to Mozambique National Legislation: Law No 4/98 of 14 January, Minesterial Diploma No 52/2010, and Law No 22/99 of May 4.

According to the Law No 22/99 of 4 May, to register a medicinal product in this country the following documents are needed [44]:

- Medical product Technical-Dossier
- CPP of the medicinal product
- Samples of the finished product and the packaging used in the Portuguese marketplace, as also the proposed mock-ups for Mozambique.

The registration is generally valid for 5 years from the date of its concession and then must be renewed. In order to maintain the medical product registered, it should be solicited its renewal at least 180 days prior to expiry the registration already granted [44].

The registration process comprises two modalities: complete and simplified registration [44]. The simplified modality is based on the recognition of a previous authorisation granted in a reference country; the complete modality is based on the submission of complete technical dossier and is required when the simplified registration is not possible [44].

Working experience

During my internship, I was involved in the registration process of various products throughout the simplified registration, since Bluepharma's medicinal products proposed for Mozambique market had already a MA in Portugal.

The first steps followed for Mozambique authorisation included:

- Request of CPPs, as previously described, in products already authorised in Portugal;
- Information/documentation regarding several CTD modules (approved by National authorities as all the products have a MA) of the product to be registered, SmPC, patient leaflet (PIL), labelling, mock-ups, carton, samples, certificate of analysis of the raw materials and finished products, GMP certificate, manufacturing licence, and MA certificate.

Subsequently, after obtaining and gathering all the previous information and documentation, I participated in the preparation of a technical dossier for each product, in Portuguese language and in accordance with the Mozambique legislation requirements. The technical dossier contains four parts [44]:

- Part I – Administrative information and characteristics of the medicine
- Part II – Chemical and Pharmaceutical Documentation
- Part III – Documentation on safety
- Part IV – Documentation on efficacy

Part I - Administrative information and characteristics of the medicine [44]

- Part I-A: Administrative Information

This section includes information concerning the type of process (complete/simplified), the proposed name for the medicine, qualitative and qualitative composition API and excipient (s), pharmacotherapeutic group, pharmaceutical form and dosage, presentation(s), shelf-life and storing condition, general classification for supply, applicant's name, address and manufacturing of finished product [44].

The information to complete this section is based on the information contained in section 3.2.P. of the CTD, in the SmPC, MA and if applicable respective variations to the MA.

- Part 1-B: Characteristics of the medicinal product
  1. Information contained in SmPC approved by INFARMED, I.P.
  2. PIL
  3. Labelling
  4. Mock-up

This information is available through the consultation of the SmPC of the medicinal product authorised in Portugal as well its PIL, labelling and respective mock-up.

Part II-Chemical and Pharmaceutical Documentation [44]

- B-l-Composition
  - Quantity and quality composition of the API and excipients

    This section is prepared according to the CTD module section 3.2.P.1 – Description and Composition of the Drug Product.
  - Description of primary and secondary packaging

    This information is available on the CTD module section3.2.P.7 – Container Closure System.
- B-2 – Manufacturing
  - Manufacturing formula
  - Description of manufacturing process and methods of control

The information to complete this section is available on the CTD module subsection 3.2.P.3.1 – Manufacture. The Batch formula is contained on the section 3.2.P.2 and the manufacturing process is detailed on the CDT module subsection 3.2.P.3.3 – Description of Manufacturing Process and Process Controls.

- B-3-Raw Materials [44]
  - Chemical description of active and excipient substance

    This section is prepared according to the CTD module section 3.2.S.1. – General Information concerning the drug substance.

- B-4 –Finished Product

  The most recent analytical certificates of the semi-finished and finished products are needed and requested to the quality control [44].

- B-5 - Stability of Finished Product [44]
  - Duration and conditions of studies
  - Number and dimension of the batches studied
  - Proposed shelf-life and storage conditions

    This data is prepared according to the information presented on the CTD module 3.2.P.8. This section of the CTD is divided in subsections that provide different information. Subsection 3.2.P.8.1 summarises the studies undertaken including conditions, batches, analytical procedures and provides a discussion of the results and conclusions of the stability studies, being also included conclusions with respect to storage conditions and shelf-life. Subsection 3.2.P.8.2 presents the post-approval stability protocol and subsection 3.2.P.8.3 includes tabulated summary of the stability results

<u>Part III – Documentation on safety</u>

In this part of the dossier, it is presented a summary regarding the product safety, including bibliographic references of publications in international credible journals [44].

To complete this part, the CTD module 2 (2.4 - Nonclinical Overview) is consulted in order to summarise the most relevant information concerning the product safety [44].

Part IV – Documentation on efficacy

This part of the dossier contains a summary of the efficacy of the medicinal product, including also bibliographic references published on credible journals [44].

The preparation of this section is based on the information included in the section 2.5 - Clinical overview of the product CTD.

To submit the requested application, all the information is printed and recorded in electronic format. At the end, all the documentation is sent to Mozambique with the medicinal products samples'.

2.2.3.3. Registration of medicines in Cape Verde

Overall requirements

Cape Verde exportation requirements are set out in the Decree-Law No 59/2006 [45]. According the Cape Verde Decree- Law 59/2006 of 15 December, the medicinal products may be imported under the provisions of the article 4 and 44 and are exempted of a MA.

Consequently, it has to be sent to the CA an application form which contain administrative information concerning the medicinal product [45], including the following elements:

- Applicant name and address
- Medicinal name proposed
- Dosage form and composition concerning active substance and excipients, including strength, presentation, route of administration, dosage and self-life.
- Therapeutic indications
- Information concerning the Manufacturer of API, excipients and finished product

In addition to the above application form, it has to be sent the following documentation:

- Copy of the MA certificate
- CPP
- SmPC, PIL and labelling approved on the country in which the medicinal product has an authorisation
- Identification of the Manufacturer, copy of GMP certificate and manufacturer's authorisation

Working experience

My function was to complete the requested application form, to compile the support documentation and to prepare a dossier compiling all this information for each product.

Those exportation-related activities were very enriching since I did not have previous knowledge in this area. Consequently, it was very challenging and stimulating to learn the legislation applicable to Cape Verde and Mozambique and understand the different requirements for each one of them.

It was possible to conclude that Cape Verde has a similar legislation to the Portuguese one. In the case of Mozambique, there are specific requirements concerning the technical dossier preparation and also administrative requirements that are not specified in the legislation and consequently are difficult to predict.

3. Discussion

3.1. Tasks assigned and learning outcomes

During my internship in the Regulatory Affairs and Pharmacovigilance department at Bluepharma - Indústria Farmacêutica, S.A., I was able to be in touch with and participate in all the Pharmacovigilance tasks/activities, as well as, in very interesting Regulatory Affairs tasks, namely those related to the registration and exportation of medicinal products in Mozambique and Cape Verde.

My curricular internship was most of the time focused on pharmacovigilance activities. I only had contact with the Regulatory Affairs activities within the scope of the above mentioned exportation processes. It was a great opportunity to understand my interest on the pharmacovigilance area.

This internship allowed me to be in contact with the real work environment and to perform different tasks that helped me to acquire and upgrade my soft and hard skills and to improve my work capability; however is a continuous learning process that will not end for sure with this curricular internship.

Hard skills

I was able to:

- Collaborate in the development and implementation of the company's pharmacovigilance system;
- Understand and to consult national and international regulation and guidelines, including GVP;
- Manage, prepare and participate in the submission process of PSURs to CA;
- Accompany and participate in the collection, collation, follow-up and reporting of ICSRs;
- Perform literature search using search techniques in worldwide databases;
- Participate in the preparation of RMP;
- Understand and participate in scientific service activities;

- Prepare and participate in the submission process of specific documentation (product dossier and support documentation and material) for the registration of medicinal products in Mozambique and Cape Verde.

Soft skills

One important skill developed was the responsibility sense since the activities performed in the department are of extreme importance and have a high impact on the company. All the activities must be performed with rigour, accuracy and attention must be paid to all the details. Hence, I learned to be more meticulous in all the processes, even in the simple ones and to pay attention to all details to try to minimise errors that may arise.

Different tasks and deadlines characterised this experience and consequently time management and organisational skills were developed. I learned to plan my days in advance and to organise my tasks/activities according with their priority/importance, in order to accomplish all of them in a quick and efficient way.

The development of verbal and written skills was also essential to discuss ideas on an assertive way as well as to prepare documentation.

Other important skill improved was self-assessment since it is essential to understand why mistakes occur, what can be improved, and the better means to overcome the gaps encountered. It is also important to have a continuous willingness to increase knowledge and skills.

During my internship, I faced new situations that contributed for improving my autonomy, critical thinking and problem solving skills. I overcame these situations by searching for solutions and discussing my ideas with my colleagues.

These capacities were, in a certain way, acquired during my academic journey due to the teaching methodology used – Problem Based Learning. This methodology requires students to be autonomous and work in team. During my Degree in Biomedical Sciences, I had tutorial sessions in which every week new problems/real life cases were discussed and solved in group. I was always encouraged to analyse, in a critical way, the problems in order to generate hypothesis and acquire information to solve them. This teaching method allowed me to be prepared for facing new situations and always look for solutions.

All the objectives initially proposed were achieved. This learning process was possible due to my Degree in Biomedical Sciences and Master's Degree in Pharmaceutical Biomedicine, which provided me a good background to conduct the assigned tasks. But also, because of the support and guidance provided by my department colleagues that were always available and in particular, the company's EU-QPPV, who guide me during all the process and contributed for acquiring new skills in pharmacovigilance and regulatory affairs area.

Over the time I gained autonomy for developing tasks in an independently way, but always being guided and supported by the department colleagues.

3.2. Difficulties

Pharmaceutical Industry is facing new challenges due to the new legislation on pharmacovigilance, which has introduced new requirements and MAH responsibilities that affect all the medicinal product lifecycle. As a consequence, the pharmaceutical companies had to begin an adaptation and adjustment period to comply with the new obligations.

Due to the new legislation, there was the necessity to develop and implement new processes and procedures and/or to review the existing ones and to train the collaborators for the new European pharmacovigilance system. The adaption process to a new legislation is not an easy process involving resources and time.

The European pharmacovigilance system suffered several deep modifications, making it even more challenging. In order to guide the different stakeholders in the implementation of the new system, it was published the Commission Implementing Regulation as well GVP. However, not all the GVP are already finished, and some of them are not yet published since they are in revision. On the other hand, EMA is not capable to fully ensure the functionality and all the expected capabilities of the European Pharmacovigilance System yet. Therefore, the pharmaceutical industry is following the new legislation requirements, but in some areas, it is needed to take into account the transitory arrangements that had suffered some modifications during my internship period.

It was not a simple process, but was very challenging, since the existing processes and SOPs in place needed to be reviewed in order to comply with the new requirements, I had

the chance to participate in their development. I also had the opportunity of seeing and collaborating in the creation and implementation of a pharmacovigilance system in a pharmaceutical company that gave me the chance to learn and develop new skills in the pharmacovigilance area.

The transition from the academic environment to the professional environment was also difficult to me since I had to adapt to a new group of people and a new place, and over the time new responsibilities arose. However, the process was easier due to the support received by all the department colleagues and the good work environment encountered.

My communication skills were also a problem to me, since I am a shy person and in that area, verbal communication skills are essential to share ideas and transmit our opinion. Although I understand that I have a long way to make, I think that I was capable to develop some communication skills and over the time became more confident in expressing my opinion.

Time management is not always simple. With time, new tasks and new responsibilities arose and it was crucial to learn to manage the time and the activities, in order to always comply with the deadlines.

4. Conclusion

This report intends to present my experience in the curricular internship describing the activities performed, the skills acquired and lessons learned during that period.

The experience in a company environment was very enriching, because it allowed me to apply the theoretical knowledge acquired during my degree in Biomedical Science as well as in my Master's Degree in Pharmaceutical Biomedicine. It was a useful complement to my academic training.

The partnerships established between the university and companies are extremely valuable since it enables that the recent graduates have contact with the working environment and establish a contact network, being that a competitive advantage to the ones that never had that experience.

This experience gave me the possibility to reflect on my weaknesses and strengths, as well as, my capability to handle with stressful and challenging real life situations, always trying to improve the less positive aspects. In addition, it contributed to analyse my work capabilities and the way I listened to the advices and placed them into practice

I believe that during my curricular internship, all the objectives laid out were accomplished and the difficulties encountered were overcame. My academic background was a useful tool to face this challenge in the best way.

In addition to the tangible outcomes summarised in soft and hard skill, this report is not enough to describe the values and advices that were transmitted to me during this period, which were precious to my personal and academic development and contributed for me to become a better professional in the near future.

In conclusion, this curricular internship was a great and useful experience, relevant to my academic and professional development and that allowed me to grow as person and as a professional. However, in this field it is essential to have in mind that it is required continuous willingness to learn and never be satisfied with ourselves.

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