Universidade de Aveiro
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Secção Autónoma de Ciências da Saúde

Pedro André Alves Jorge

Internship Report: Experience in Bluepharma's pharmacovigilance sector

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Relatório de estágio apresentado à Universidade de Aveiro para 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 da Professora Doutora Alexandra Isabel Cardador de Queirós, Professora Coordenadora Sem Agregação da Escola Superior de Saúde da Saúde da Universidade de Aveiro.

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presidente	Professor Doutor Nelson Fernando Pacheco da Rocha Professor Catedrático, Universidade de Aveiro
arguente principal	Doutor Bruno Miguel Alves Fernandes do Gago Professor Auxiliar Convidado, Universidade de Aveiro
Orientador	Professora Doutora Alexandra Isabel Cardador de Queirós Professora Coordenadora S/ Agregação, Universidade de Aveiro

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palavras-chave

Universidade de Aveiro; Biomedicina Farmacêutica; Bluepharma; Medicamento; Farmacovigilância; Segurança; Regulamentar;

resumo

O presente relatório descreve um estágio curricular no âmbito do mestrado em Biomedicina Farmacêutica da Universidade de Aveiro realizado ao longo de dez meses no sector de farmacovigilância da empresa farmacêutica Bluepharma – Indústria Farmacêutica, S.A.

Os profissionais da Biomedicina Farmacêutica, no âmbito da sua formação, desenvolvem conhecimentos de conceitos teóricos e processuais associados à farmacovigilância (ciência relacionada com a segurança de medicamentos). Os objetivos deste estágio previam a colocação em prática desses conhecimentos, bem como a aquisição e aprofundamento de conhecimentos relacionados com as matérias de farmacovigilância e segurança de medicamentos de uso humano em contexto profissional.

O relatório encontra-se dividido em quatro partes. Numa primeira parte são descritos os objetivos deste estágio e o estado-de-arte da farmacovigilância. Uma descrição das atividades envolvidas neste estágio é apresentada na segunda parte, seguida da sua discussão na terceira parte. Por fim, é apresentada uma conclusão onde são discutidos os principais conhecimentos adquiridos e qual importância da experiência académica para complemento da formação.

keywords

University of Aveiro; Pharmaceutical Medicine; Bluepharma; Medicinal product; Pharmacovigilance; Safety; Regulatory;

abstract

The present report is intended to describe a ten-month internship for the master degree in Pharmaceutical Medicine in University of Aveiro performed in the pharmacovigilance sector of the pharmaceutical company Bluepharma – Indústria Farmacêutica, S.A.

Pharmaceutical Medicine professionals, based on their background, have knowledge about theoretical and procedural concepts related to pharmacovigilance (the science responsible for the study of safety of medicinal products). The objectives of this internship forecasted the application of this knowledge, as well the acquisition and improvement of knowledge related to the pharmacovigilance and medicinal products' safety in a professional setting.

This report is divided in four sections. In section one a description of internship objectives and current state-of-art of pharmacovigilance is presented. The activities performed during this internship are described on section two, followed by their discussion on section three. Finally, section four presents a conclusion analysing the main skills and knowledge gained during this internship and their relevance for complementing academic experience.

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LIST OF ABBREVIATIONS

ADR – Adverse Drug Reaction

AE – Adverse Event

BA/BE – Bioavailality/Bioquivalence

CHMP – Committee for Medicinal Products for Human Use

CIOMS – Council for International Organizations of Medical Sciences

CMDh – Co-ordination group for Mutual recognition and Decentralised procedures – human

CTD – Common Technical Document

EC – European Commission

eCTD – Electronic Common Technical Document

EEA – European Economic Area

EMA – European Medicines Agency

EMAS – Eco-Management and Audit Scheme

EU – European Union

EU-QPPV – Qualified Person responsible for Pharmacovigilance

GVP – Good Pharmacovigilance Practices

HMA – Heads of Medicines Agencies

ICH – International Conference on Harmonisation

ICSR – Individual Case Safety Report

ISO – International Organization for Standardization

MA – Marketing Authorization

MAA – Marketing Authorization Application

MAH – Marketing Authorization Holder

NCBI – National Center for Biotechnology Information

OHSAS – Occupational Health and Safety Advisory Services

PhSMF – Pharmacovigilance System Master File

PQ&C – Product Quality & Compliance

PRAC – Pharmacovigilance and Risk Assessment Committee

PSUR – Periodic Safety Update Report

RMP – Risk Management Plan

SAP – Systems, Applications & Products

SmPC – Summary of Product Characteristics

SUE – Serious Undesirable Effect

US/USA – United States of America

WHO – World Health Organization

1 INTRODUCTION

In order to accomplish my curricular plan for Master degree at University of Aveiro's Trainning Program in Pharmaceutical Medicine, I performed a ten-month internship at Bluepharma's Regulatory Affairs & Pharmacovigilance Department, more precisely on its Pharmacovigilance sector. The present report is intended to describe this experience.

1.1 Objectives

My ten-month internship at Bluepharma's *Regulatory Affairs & Pharmacovigilance* department had three main objectives (also subdivided):

1. To obtain and develop *skills* related to the pharmacovigilance field:
    - To be familiarized with the most relevant pharmacovigilance activities in European Economic Area (EEA);
    - To understand EEA pharmacovigilance requirements;
    - To understand the role of pharmacovigilance in the maintenance of medicines marketing authorizations (MA).

2. To obtain and develop skills related to regulatory affairs:
    - To get knowledge about EEA pharmaceutical legislation framework;
    - To obtain a deeper understanding on the applicability of the European and Portuguese pharmaceutical legislation framework.

3. To acquire experience within the regulatory affairs field inside a pharmaceutical company:
    - To be integrated within company's projects;
    - To observe how communication flows throughout the various sectors within a pharmaceutical company;

- To develop critical judgment about established (or to be established) procedures;
- To observe the assessment of the compliance between what is written (e.g. Standard Operating Procedures) and what is performed;
- To observe how communication with the authorities is established and maintained.

1.2 Report Structure

This report is divided in four sections. In this section, *Introduction*, I described my objectives for this curricular internship, current state-of–the-art of drug development and pharmacovigilance, and main challenges faced by pharmaceutical companies in EEA due to the new pharmacovigilance legislation. Also, in this section I made a short description of the host company. Internal training sessions and working experience were described in section two. The accomplishment of proposed objectives was discussed on section three. In the last section, I presented the main conclusions and outcomes of this internship and related it to my academic background.

1.3 State of the Art

Pharmaceutical Medicine is a medical science that can and should be involved in the various stages of medicinal products lifecycle. Since the initial stages, related to product's discovery and development, throughout its licensing and post-marketing stages, Pharmaceutical Medicine professionals are involved in a variety of activities with the final goal to provide safe and effective medicines to the public (1). In this section I will describe the traditional life-cycle of a medicinal product and make a succinct state-of-the art of pharmacovigilance, where most of my internship activities were focused.

1.3.1 Product Life-Cycle

A medicine is a living and dynamic entity which life-cycle begins when a company decides to develop it and lasts until the moment it is withdrawn from the market. The cycle starts with the development of the product, which can encompass pharmaceutical, non-clinical and clinical development depending on the type of product, followed by authorities' approval. After the product launch into the market, where it finally become available to the patients, a phase characterized by an increase in sales generally occurs, motivated not only for the novelty factor that usually is linked to the marketing of a New Chemical Entity, but also for the extensive promotion plan that any given company will put in place in the very first years of marketing. It then follows a maturity phase, where the product sales stabilize. The final phase is designated by Decline phase and it is characterized by a significant decrease in product's sales (see Figure 1) (2).

In this section, details are provided regarding the following stages of a medicinal product life-cycle:

- Product Development;
- Marketing Authorization;
- Decline phase.

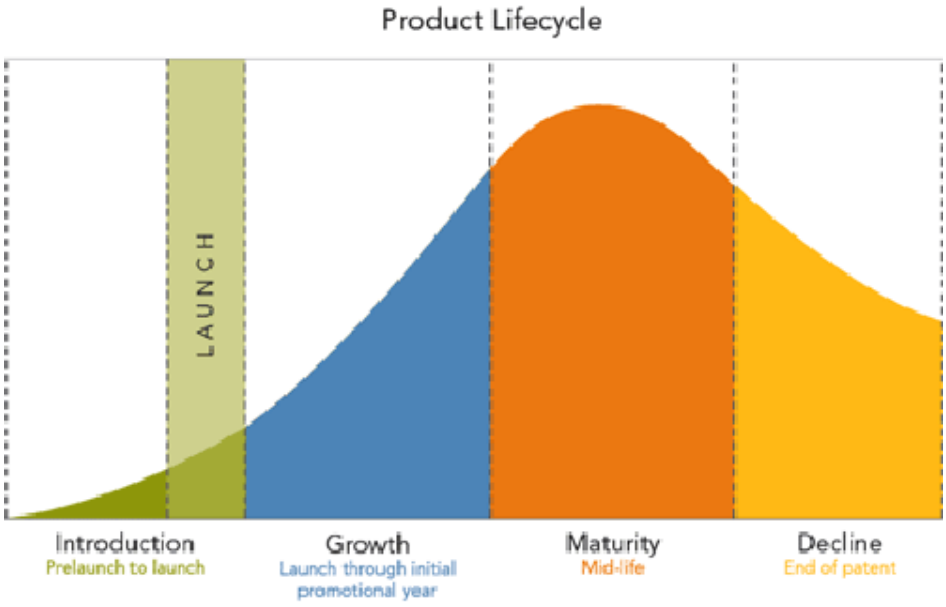

Figure 1 – Medicinal product life-cycle (image taken from: http://www.soopertutorials.com/wp-content/uploads/2009/03/market-stages-thumb.gif)

Product Development

A medicinal product, as any other product intended to be marketed, starts its life-cycle, after it is discover, with the development phase. This is a long and costly process. It can pass more than ten years since the beginning of pre-clinical studies until the medicine finally receives the marketing approval and the development costs may easily arise to the millions of dollars, sometimes even billions. Attrition rates are also high, with only one over tens of thousands compounds found during screening phase reaching the market (see Figure 2). (2).

As shown in Figure 2, the pre-clinical phase comprises the studies used to identify the potential lead compounds for clinical studies. During this phase, through *in vitro* (e.g target identification, target validation…) and *in vivo* studies (e.g toxicology studies, safety studies…) the potential for a chemical entity to interact with an identified biological target and its safety are evaluated (2, 3).

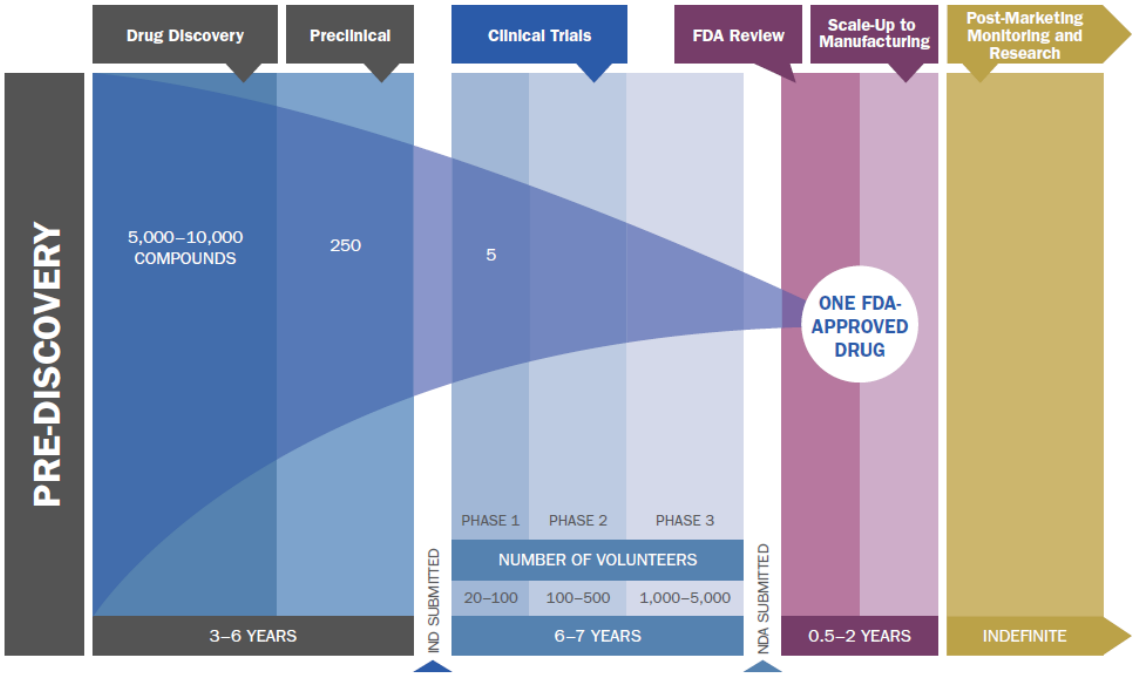

Figure 2 – Phases involved in drug discovery process (image taken from PhRMA Industry Profile 2012)

Within the traditional model, the clinical development of a new medicine generally consists in four phases (4). Phases I to III comprises a battery of studies in humans needed for approval. Phase IV includes a number of studies that are normally undertaken after MA. The main features of each phase are presented on Table 1 (1, 4):

Table 1 – Clinical development phases (1, 4)

Type of Study	Main Features
Phase I (or Human Pharmacology studies)	• First in human trials • Evaluation of medicine's tolerability; • Describe main pharmacokinetics and pharmacodynamics characteristics; • Determine drug interactions; • Estimate activity; • Healthy volunteer; • 30 to 50 subjects;
Phase II (or Therapeutic Exploratory studies)	• First studies on the target population; • Dose estimation; • Scientific basis for trial design of larger clinical trials; • 250 to 500 subjects;
Phase III	• Determine drug's efficacy;

Type of Study	Main Features
(or Therapeutic Confirmatory studies)	• Determine the safety profile; • Dose-response relationship • Scientific basis for regulatory evaluation during marketing authorization application; • Over one thousand patients exposed;
Phase IV (or Therapeutic Use studies)	• Improvement on the benefit-risk profile of the medicine (general and/or special populations); • Evaluation of the medicine under marketing conditions; • Identification of rare and very rare ADRs; • Optimize dosing recommendations; • Over ten thousands patients exposed;

However, due to their relevance for product development, some studies usually considered to be part of a specific phase can be conducted in other distinct phases (see Figure 3).

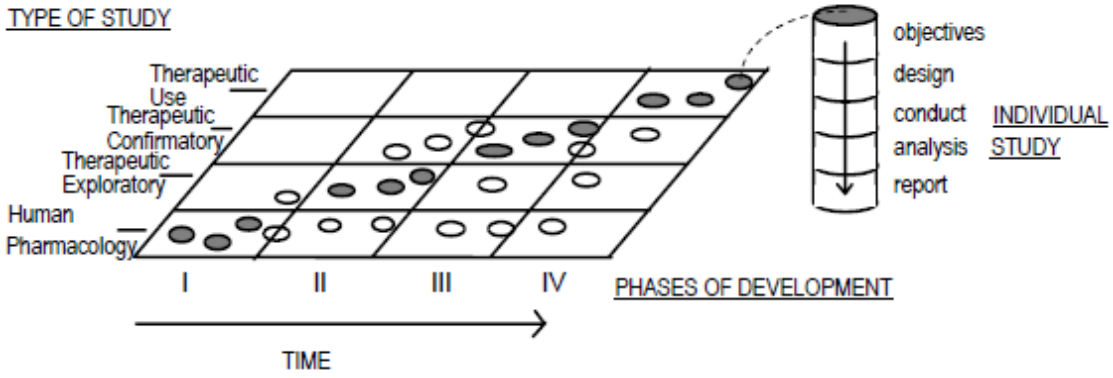

Figure 3 – Relationship between type of study and phase of develoment (4)

This model is the usually followed for the development of new medicines. When a company intends to obtain a MA for a generic medicine clinical studies must be underwent also. However, the clinical program required is considerably streamlined.

Since in this phase the efficacy and the safety profiles of the reference medicinal product are already well studied, there is no longer the need for a company to develop an extensive clinical plan. As referred on article 10(a) of Directive 2001/83/EC, generic medicinal products must prove that they are bioequivalent to their reference medicinal products. In order to accomplish this

purpose, companies shall conduct Bioequivalence/Bioavailability (BA/BE) studies (5).

A BA/BE study is intended to demonstrate that a given investigational medicinal product is pharmaceutically equivalent to a medicinal product already in the market (referred as Reference medicinal product). Two products are considered pharmaceutically equivalents if bioavailability parameters (such as Peak Concentration or Area Under the Curve) are within a certain range (normally between 80% to 125%). If bioequivalence is proved, that will mean that both products have the same safety/efficacy profile and risk-benefit ratio (6).

Although in my internship the thematic of innovative drugs development and its lifecycle has been approached for several times, the scope of my activities was always focused on the generic medicinal products. I had the opportunity to be involved in a wide range of pharmacovigilance activities related to the approved generic medicinal products and with some safety activities specifically related to the development of generic medicinal products.

Marketing Authorization

After successfully complete the investigational/development plan for a medicine, the next logical step for a company is its placement on the market, either on its own name or through license agreements. In order to have a product on the market under its name, any given company has to apply for a marketing authorization – Marketing Authorization Application (MAA). MAA process involves the submission of a dossier containing all the relevant administrative data/prescribing information and required technical/scientific data:

- Pharmaceutical data
- Non-clinical data
- Clinical data

On International Conference on Harmonisation (ICH) regions (European Union (EU), United States of America (USA) and Japan), as well as on other countries that recognize ICH standards, the structure of the above mentioned dossier is well established and is known as Common Technical Document (CTD). CTD

represents a harmonized way to submit the information related to a medicinal product in the three ICH regions. This dossier should contain the most up-to-date technical and scientific information related to the medicine.

As presented on Figure 4, CTD's structure has five individual modules on its structure (7):

- **Module 1: "Administrative Information and Prescribing Information"** – this module should contain all regional-specific documentation necessary for the marketing authorization, such as application forms and labels. Due to its regional nature, this is the only CTD module that contains distinct information in all three regions;
- **Module 2: "Common Technical Document Summaries"** – this should be an introductory module where the medicinal product is presented, and an overview of its technical and scientific features is made;
- **Module 3: "Quality"** – this is the section dedicated to description of product's technical features, such as manufacturing process, stabilities, specifications and quality controls;
- **Module 4: "Nonclinical Study Reports"** – in this section, a compilation of all non-clinical studies relevant to the safety and efficacy of the medicinal product is made;
- **Module 5: "Clinical Study Reports"** – this module contains the information related to the studies made on humans;

As already referred in this section, besides from BA/BE studies, a MAA for a generics do not require the submission of non-clinical and clinical study results. In practice this will lead to the submission of simplified CTDs, where module 4 and some sections of module 5 are suppressed (8).

After a MAA had been approved, the medicine can finally be marketed. However, the Marketing Authorization Holder (MAH) still has to comply with several requirements in order to maintain the MA. Those requirements are intended to constantly evaluate and maintain the safety and efficacy balance during daily practice. A generic medicine must keep up-to-date the scientific information with the reference medicine (5) and with the applicable technical-scientific and legal requirements.

During my internship I had the opportunity to contribute to the elaboration of the following relevant documents for more than one CTD, within the scope of EU MAA:

- 1.3.1 – Proposed prescribing information (Summary of Product Characteristics (SmPC) and Package Leaflet)
- 1.8.1 – Update documentation related to PhSMF
- 1.8.2 – Risk Management Plans
- 2.5.6 – Addendum to clinical overview (during renewals)

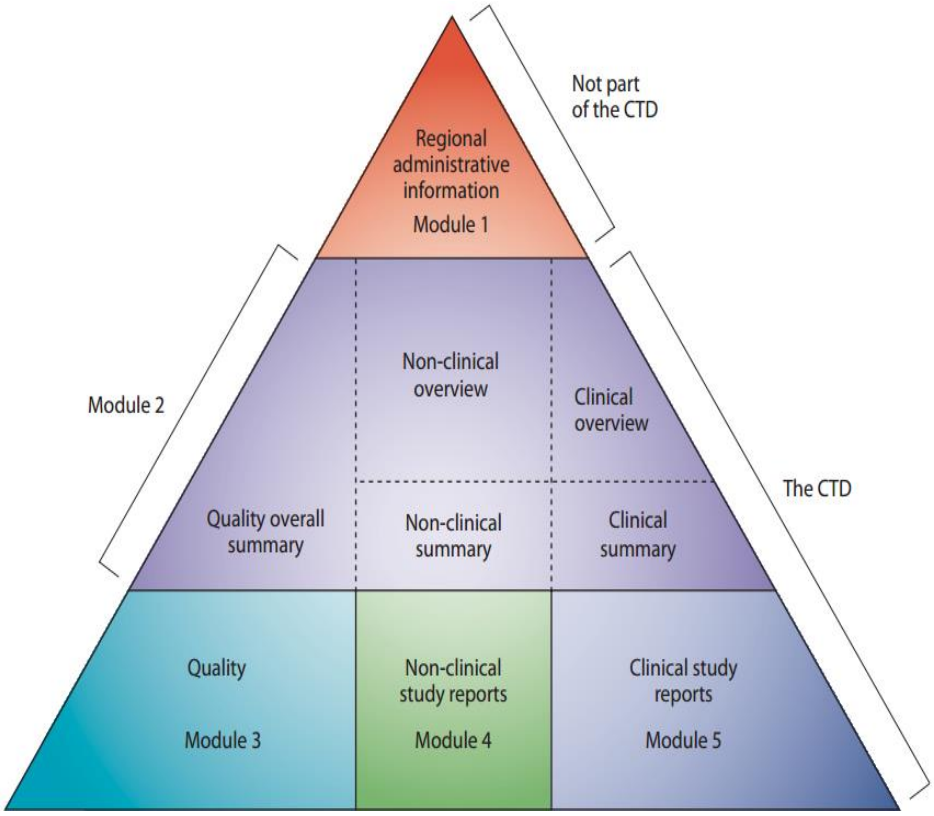

Figure 4 – CTD structure (image taken from http://www.ich.org/products/ctd.html)

The MA, except in special cases determined by the authorities, has to be renewed after the first five years. During the submission of the renewal, the MAH should provide an overview of the first five years on the market. After the renewal approval the MA will have unlimited validity (5).

In what specifically concerns to the safety, the renewal applications requires a critical assessment of product's safety profile in the five-year period. Therefore, an addendum of the clinical overview (Sub-module 2.5) should be prepared and submitted as part of the renewal application. During renewal procedures,

reference information of generic medicines should be updated to in line with reference product's information.

During my internship, I had the opportunity to collaborate in the assessment of approved SmPC and Package Leaflets and to be involved on the preparation of addendums of clinical overviews.

Decline phase

Decline phase refers to the phase when products sales decreases after reaching maturity (this is a phase when sales are stabilized). For innovative products this generally starts to happen when its market exclusivity period ends and/or patent are off, which ends with any protective measures against the generic medicinal products. As stated in Article 10 of Directive 2001/83/EC, in the EEA generic medicines can only be marketed ten years after the innovative product approval (marketing exclusivity period).

MAAs for generic medicinal products can start to be submitted eight years after the first MA for the innovative product in the EEA (data protection period), however those products can only be placed on the market ten years after the innovative product's MA.

1.3.2 Pharmacovigilance

Pharmacovigilance concerns to the science responsible for studying safety issues related to the medicines use (9). Etiologically, pharmacovigilance is the combination of the Greek word *pharmakon* (meaning drug) with the Latin word *vigilare* (meaning keep watch). The first appearance of this term on scientific literature occurred in 1974 by Dunlop D (10), however the roots back to 1960s, decade with the scandal related to thalidomide's use by pregnant women.

Pharmacovigilance is defined as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem" (11). It has the objective to provide to health care professionals and general public the most recent data and conclusions regarding the safe use of medicines.

History

As referred previously, pharmacovigilance has its roots in the 1960s following the thalidomide's scandal. After this episode it became clear that the legislation at that time did not provided adequate protection to patients against medicines' harmful effects. It was necessary to introduce new safety and efficacy criteria for the approval of new medicinal products (9).

Concomitantly to the need of establishing new criteria for marketing approval, it was also identified the need for MAHs and authorities to implement effective post-marketing surveillance system aiming the detection as early as possible the occurrence of Adverse Drug Reactions (ADR) related to the medicine (9).

During the sixteenth World Health Organization (WHO) general assembly, in 1963, it was defined that a surveillance system for ADRs in a global level should be implemented. Currently, this system is based in the Swedish Uppsala Monitoring Centre and WHO is responsible for its maintenance. Some of the most important moments that lead to its creation were the following ones (12):

- In 1968, the *WHO Pilot Research Project for International Drug Monitoring* was created;
- In 1971, the *WHO International Drug Monitoring Programme* was created;
- In 1978, Uppsala Monitoring Centre was established as base for WHO surveillance system;
- VigiBase creation in mid 1990s.

Another important moment in pharmacovigilance history is the creation in 1949 of the Council for International Organizations of Medical Sciences (CIOMS). This entity had the objective to create, facilitate and promote international activities in the field of biomedical sciences. Medicines' safety was one of the topics for which CIOMS published guidance documents. These guidance documents describe in detail how MAHs should perform their activities, either in pre-authorization either in post-authorization phases (13, 14).

In Europe notable changes on pharmacovigilance field were observed since 2001. Following the publication of the "Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use" (hereafter referred Directive 2001/83/EC) member states should have implemented pharmacovigilance systems in order to collect safety information related to marketed medicines and to evaluate such information in a scientifically way, as stated on Article 102 (5).
Within this directive MAHs were obligated to have in their pharmacovigilance systems a Qualified Person responsible for Pharmacovigilance (EU-QPPV). As present on Article 107, EU-QPPV is responsible for (5):

- Creation and maintenance of the pharmacovigilance structure and system of a company;
- Supervising all pharmacovigilance collaborators of Bluepharma. The QPPV is responsible for assign specific task to the pharmacovigilance collaborators and for their appropriate training;
- Pharmacovigilance System Master File maintenance;
- Having an overview of medicinal product safety profiles and any emerging safety concerns;
- Having awareness of risk minimisation measures;
- Ensuring that all suspected ADRs reported to MAH are recorded and analysed scientifically;
- Preparation of reports to be sent to authorities;
- Ensuring that any request of the authorities related to the safety of the medicine is promptly satisfied;
- Provision of any other information relevant to the benefit-risk evaluation of a medicine;
- Supervising all pharmacovigilance collaborators of Bluepharma. The QPPV is responsible for assign specific task to the pharmacovigilance collaborators and for their appropriate training;

Another important reform introduced by the Directive 2001/83/EC was the creation of an European system allowing a faster exchange of pharmacovigilance data between European competent authorities. As present

on Article 105, this system is known as Eudravigilance and European Medicines Agency (EMA) is responsible for its development and maintenance (5).
In 2004, aiming to improve and harmonize European procedures applied in the pharmacovigilance activities, European Commission (EC) approved the Regulation No. 726/2004 of 31 March 2004. This regulation established the roles and responsibilities for the several stakeholders involved in pharmacovigilance activities within EU.

A new revolution in European pharmacovigilance legislation occurred between 2010 and 2012. In this period the following legislative acts, amending Directive 2001/83/EC and Regulation No. 726/2004, were approved by EC:

- Directive 2010/84/EU of 15 December 2010 – amending Directive 2001/83/EC in order strengthen EU law in pharmacovigilance;
- Regulation (EU) No. 1235/2010 of 15 December 2010 – amending and Regulation No, 726/2004 in order strengthen EU law in pharmacovigilance;;
- Commission Implementing Regulation (EU) No. 520/2012 of 19 June 2012 – provisions on the implementations of MAHs' pharmacovigilance systems and provisions about the content and transmission of ADR reports, RMPs, PSURs and Post-Authorization Safety Studies;
- Directive 2012/26/EU of 25 October 2012 – clarifying and strengthen EU actions related to safety concerns (e.g. Article 31 referrals, Urgent Union procedures);
- Regulation (EU) No. 1027/2012 of 25 October 2012 – provisions about the list of medicinal products that are subject to additional monitoring and the procedure to be followed by MAHs when suspending, withdrawing or not renewing an MA.

This reform was made in order to improve and strengthen European pharmacovigilance network, to improve communication with healthcare professionals and to enhance the participation of healthcare professionals and society in general in the discussion of medicinal products safety. Also the roles and responsibilities of all parties involved were adapted in order to accomplish these objectives (15, 16).

In order to comply with Article 108a of Directive 2001/83/EC, as emended by Directive 2010/84/EU, EMA developed in cooperation with other competent authorities and other interested parties a series of guidance documents to help MAHs and competent authorities implementing pharmacovigilance requirements (5, 17). Those documents are known as Good Pharmacovigilance Practices (GVP). Since July 2012, when the first seven modules related to prioritised processes were released, EMA launched thirteen of a total of sixteen GVP modules. (17).

Following the publication of Regulation (EC) No. 726/2004, as stated in Article 55, EMA became responsible for the coordination of all scientific resources available in all Member States regarding the evaluation, supervision and pharmacovigilance of medicinal products in EEA. Pharmacovigilance and Risk Assessment Committee (PRAC) was established in July of 2012 in order to support the Committee for Medicinal Products for Human Use (CHMP) activities related to safety issues (18, 19). PRAC mandate covers the following procedures (19, 20):

- Supervision of all aspects related to the risk management of the use of medicines (e.g. Periodic safety update reports (PSUR) evaluation and signal detection and evaluation);
- Evaluation of protocol and results of post-authorisation safety studies;
- Advice about Eudravigilance database functionalities;
- Advice about medicines under additional monitoring;
- Recommendations about pharmacovigilance issues at request of CHMP and CMDh.

Pharmacovigilance presents over fifty years of history. It is a science that emerged from the need for better safety conditions when using medicinal products. Over this period several reforms occurred in this field focusing public health protection. Individualising the European case, in recent years several major reforms took place in order to adapt current demands for safe medicinal products, reshaping the roles of MAHs, authorities and civil society to accomplish this purpose.

1.3.3 Adverse Drug Reactions

As referred previously, the beginning of pharmacovigilance is based on the thalidomide's scandal. In the beginning of 1960's decade, reports of several birth defects related to thalidomide's use, especially phocomelia, make people questioning about the safety of this medicine. In the case described, phocomelia reactions on new-borns were the element that made possible to evaluate the thalidomide's safety. These elements are called ADRs.

According to the current definition, an ADR is "*a response to a medicinal product which is noxious and unintended*" (5). Concerning the "*response to a medical product*" it should be referred that this response should present a causality relation with the medicinal product use (clearly established by scientific methodologies) (21).

According to Article 2 of the Directive 2001/20/EC, an AE is "*Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment*" (4, p4), (22). Therefore, reports of adverse reactions really caused by the medicine and reports adverse events can occur when using a medicinal product.

According to the Module VI of GVPs, AE received should only be validated by determining (23): the identity of reporter; an identifiable patient; an identifiable medicine identifiable; and a suspected reaction.

After these elements had been fully validated the causal relationship between AE and medicinal product can be then evaluated. In the case of a positive causal relationship of an AE received by the sponsor, the reaction may or may not be reported the authorities, depending on its seriousness assessment (24). In a following section this process will be described in more detail.

Based on the seriousness, and ADR can be classified as serious or non-serious. An ADR is classified as serious if one of the following outcomes occurred:

- Death;
- Life-threatening condition;
- Requires inpatient hospitalisation or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;

- Congenital anomaly/birth defect.

Any other ADR that result in other outcomes and not above mentioned, it should be classified as non-serious.

In the industry, other important classification systems used are those related to causality assessment. One the most used causality system is the Naranjo's scale. According to the causal relation of the ADR with the suspected medicinal product, the ADR can be classified into (25):

- Definite
- Probable
- Possible
- Doubtful

In a more academic view, ADRs can be classified on several types, depending on the relation with the dose and/or the onset of the reaction. One on the most widely used classification system categorizes ADRs on seven types: from type A to type F as described in Table 2 (26).

Table 2 – Classification of adverse drug reactions **(26)**

Type of reaction	Features
A: Dose-related (Augmented)	Common Related to a pharmacological action of the drug Predictable Low Mortality
B: Non-dose-related (Bizarre)	Uncommon Not related to a pharmacological action of the drug Unpredictable High Mortality
C: Dose-related and time-related (Chronic)	Uncommon Related to the cumulative dose

Type of reaction	Features
D: Time-related (Delayed)	Uncommon Usually dose-related Occurs or becomes apparent sometime after the use of the drug
E: Withdrawal (End of use)	Uncommon Occurs soon after withdrawal of the drug
F: Unexpected failure of therapy (Failure)	Common Dose-related Often caused by drug interactions

As conclusion, when using a medicinal product deleterious effects may occur that might or might not be related to the medicine. The knowledge of the occurrence of such adverse reactions may change the safety profile of a medicinal product. Those changes may lead to a shift in risk-benefit ratio. When this occur, MAHs need to preform appropriate actions in order to re-assure a positive risk-benefit ratio, which my pass through a simple update of products information to withdraw the product from the market. Therefore, MAHs should be aware of the occurrence of safety issues related to their products.

1.4 Host Company – Bluepharma

Bluepharma – Indústria Farmacêutica, S.A., hereafter referred as Bluepharma, history starts in February of 2001, after the acquisition of a Bayer's industrial unit. Bluepharma is a Small and Medium Enterprise based in Coimbra. Blupharma's activities are centralized in three main fields:

- Producing pharmaceutical drugs for Bluepharma and other companies;
- Research, development and registration of pharmaceutical drugs;
- Marketing of generic pharmaceuticals.

Figure 5 – Bluepharma's building

In the last thirteen years, several moments have contributed to the sustainable growth of Bluepharma. Some of the most important were the following:

- Foundation of Bluepharma Genéricos – Comércio de Medicamentos, S.A., in 2002 – responsible for the commercialization of medicinal products under Bluepharma brand;
- Inauguration of the Research and Development Center, in 2003 – Bluepharma gained the ability to manufacture new products within its facilities;

- Certifications of ISO 9001, 14001 OHSAS 18001 and EMAS, in 2003 – first Portuguese pharmaceutical company to acquire integrated certification;
- Launch of the first medicine developed at Bluepharma, in 2008 - ;
- Food and Drug Administration certification, in 2009 – first Portuguese pharmaceutical company allowed to produce medicinal products for US market;
- Inauguration of Bluepharma's new facilities, in 2010 – allowed an increase of Bluepharma's activities;
- Inauguration of Blueclinical, 2012 – allowed Bluepharma to extend its development activities and to sponsor its own clinical studies.

As above mentioned, in 2002 Bluepharma Genéricos – Comércio de Medicamentos, S.A. (thereafter referred as Bluepharma Genéricos) was founded. Bluepharma Genéricos holds the MA of the most part of the Bluepharma group portfolio in Portugal. Currently, Bluepharma Genéricos has a portfolio with nearly seventy generic medicinal products, and it is a distributor for two medical devices and one cosmetic product.

Bluepharma portfolio only includes nearly ten products. Therefore, Bluepharma's Pharmacovigilance activities are mainly related to Bluepharma Genéricos products.

Bluepharma group also includes companies related to the development of innovative products. Luzitin, SA and Treat-U are two spin-offs related to the development of new alternatives to oncology treatments. These spin-offs derived from the close relationship with the academia, which was one the factors that were on the genesis of the creation of the Bluepharma.

Bluepharma structure comprises several distinct departments. During my internship I was allocated to Regulatory Affairs & Pharmacovigilance. This department is responsible for:

- Submission and management of MAA;
- Management of approved MA;
- Support activities related to the marketing of medicinal products;
- Preparation of regulatory documentation;

- Pharmacovigilance;
- Scientific Service;
- Cosmetics and Medical Devices registration and dossier management.

2 INTERNSHIP EXPERIENCE

My experience in Bluepharma was focused on the activities performed in Regulatory Affairs & Pharmacovigilance Department, in particular the activities related to pharmacovigilance. However, I had the opportunity to learn the activities performed in other departments. Either by participating in companies activities either by attending to in-house training sessions, I had contact with several other departments of Bluepharma. In this section, I will start to describe my internal training program during my internship. In sub-section 2.2 I will describe the pharmacovigilance activities in that I was involved. In sub-sections 2.3, 2.4 and 2.5 I will describe the activities related to regulatory affairs, cosmetics and scientific service, respectively, in which I participate.

2.1 Experience on Several Departments of Bluepharma

As referred in the previous section, Bluepharma has several certifications. In order to comply with some requirements necessary to maintain those certifications, Bluepharma's collaborators have to attend to several specific training sessions. Therefore, during my internship I attended to several in-house training sessions, some of them mandatory and others inserted in my own training program. Moreover, this allowed me to follow the activities developed in several departments for one day, besides Regulatory Affairs & Pharmacovigilance department.

As any other new collaborator in Bluepharma I started my internship in Bluepharma by reading Bluepharma's integration manual for new collaborators, where a description of Bluepharma is made and general internal rules are described. Also, I attended to a one-day training session involving the following themes:

- Bluepharma's Quality Management System;
- Innovation and Research and Development certification;
- Environment and safety management system;

- Good Manufacturing Practices;
- CTD contents and regulatory requirements;
- Information technology services;
- Pharmacovigilance.

As referred before, I had the opportunity to follow the activities several Bluepharma's departments:

- Research and Development
- Business Development
- Production and Packaging
- Quality Control
- Product Quality & Compliance
- Quality Management

In this section I will describe the learnings obtained during these training sessions.

2.1.1 Research and Development

Located in the Research and Development building, the this department encompasses several activities related to the manufacture of new products and with post-marketing related activities. The department is structured in three different sections:

- **Galenical development** – responsible for the development of new products at a sub-industrial scale, by testing several formulations;
- **Analytical development** – responsible for the Bioavailablity studies for new Bluepharma's products;
- **Stabilities** – responsible for testing Bluepharma's products under several ICH stability conditions necessary for MAA and shelf-life data.

In this training session I had the opportunity to be in contact with the laboratory activities performed within a pharmaceutical company. This allowed me to understand their relevance for medicinal products quality.

I also had the opportunity to obtain a better understanding on some concepts that I generally observe on medicinal products dossier, such as the dissolution

profile, and their relevance during the development of new generic medicinal products.

During this training session, I noted that this is a very crowded environment, with several people occupying a large section of laboratory benches. Although it may appear a cluttered environment, I had the chance verify that every person and every equipment has specific tasks and that laboratory chiefs manage their activities.

2.1.2 Business Development

I had the chance to attend a training session in Bluepharma's Business Development department. During this training session I learned what Bluepharma's business pillars are. The three main business areas developed in Bluepharma are: Licensing of technology (either by the acquisition of technologies external to Bluepharma the so called "licensing-in", or by Licensing-out, this is by licensing its own developed technology), by exporting its own brand and branded products through distribution contracts and also gathering manufacture contracts that allow Bluepharma to handle and manufacture at Bluepharma's facilities third party products as a service. This business area is commonly referred in the pharma industry as Contract Manufacturing or Third Party Manufacturing. This last business area is still one of the key business activities of Bluepharma in the present day.

I also learned that the Business Development department has a very transversal role in the research and development activities associated to a specific project. The influence of the department depends very much on which stage of product development the project is. These activities vary from Intellectual Property review and screening, procurement of active pharmaceutical ingredient manufacturers during development phase, to find partners during clinical and application phase to whom license the product or even to search for joint ventures or co-development opportunities to take place between Bluepharma and a 3rd party in order to mitigate risks and costs allocated to a specific project or simply to strengthen it by exploring synergies between different companies.

The Business Development department is also responsible for the application for reimbursement of the new products intended to the Portuguese market.

My experience in Business Development Department allowed me to conclude that this is a very pro-active department, since persons working in this department are expected to find and maintain new business opportunities for Bluepharma. Also, in contrast with my expectations, a broader range of activities a related to this department. However, as I observe during daily practice, the activities performed by Business Development department most of the time require regulatory support, which requires constant contact between the two departments.

2.1.3 Planning and Production Management – Panning and Purchasing

Planning and Production Management department is responsible for planning how orders received from customers are to be managed.

Planning and Production Management department structure encompasses two distinct sectors:

- **Planning and Purchasing** – responsible for contact with Bluepharma's customers and suppliers;
- **Production Management** – responsible for the management of production activities and equipment maintenance.

In this section I will only describe my learning related to the first sector (Planning and Purchasing). Production Management activities will be presented on section "Planning and Production Management – Production Management".

During my training session in this sector I had the opportunity to observe how a new order received from a costumer is processed. After a new order is received by Planning and Purchasing sector a new entry is created on Systems, Applications & Products (SAP) software. This software system, by analysing the records of raw materials present in Bluepharma at the time, generates an alert, listing the raw materials that exist and those that are missing to fulfil the order.

It is responsibility of Planning and Purchasing sector to manage the stock of raw materials in Bluepharma. Therefore, when a raw material is missing a member of this sector will enter in contact with suppliers in order to obtain the needed raw material.

As I observed, some raw materials have a short shelf-life and therefore there is only a small window of opportunity to be used during production activities. This means that Planning and Purchasing and Production sectors should have their activities coordinated in order to maximize the use of those raw materials and avoid the loss of resources.

For raw materials that are used in a huge set of production activities, or have a long shelf-life, their stock should be maintained stable throughout production activities. I observed how these stocks of raw materials are managed and understand the implications of their missing. If they are missing, several productions activities may be delayed, which could have impact on Bluepharma's future contracts.

Defining the final format of packaging materials (primary and secondary) is one the activities performed by this sector. I had the opportunity to observe how this activity is performed. When a new product is intended to be packaged in Bluepharma, packaging dimensions have to comply with client's standards and feasible to be packaged with Bluepharma's equipment. To accomplish this, a series of draft versions, known as "proofs", is exchanged between Planning and Purchasing and client representatives, until a final version is agreed. An entry with this final version is created on SAP system that will be accessed by packaging when preforming their tasks.

This training session allowed me to be in contact with raw materials stock management inside a pharmaceutical company. I got the chance to understand the importance of centralizing this service inside a company, since it can save resources by obtaining better supplying contracts. Also, I observe how final format of packaging materials is obtained. This training session also allowed me to understand how regulatory activities that I perform in my daily practices may affect the activities of other departments. This department presented me a very dynamic team since all members have to coordinate their tasks between them

and Production and Packaging sectors in order to comply with clients' orders on time.

2.1.4 Planning and Production Management – Production Management

As referred above, Planning and Production Management department is divided is two distinct sectors. Production Management sector encompasses activities related to production, packaging and equipment maintenance.

During my internship I had the opportunity to attend to training sections related to the production and packaging of medicinal products in Bluepharma. Although I did not have contact with equipment maintenance activities, in a presentation explaining Planning and Production Management department's activities, I got the chance to understand that these activities are related to production and packaging equipment maintenance. Also, the maintenance crew is responsible for adapting Bluepharma's machinery in order to comply with special requests from clients, such as special marks on tablets.

In this sector I attended to training sessions related to production and packaging activities performed by Bluepharma.

Bluepharma is licensed to produce several types of pharmaceutical forms. This includes: tablets, film-coated tablets, orodispersible tablets, hard capsules and oral liquids.

During this training session I observed that Bluepharma's production equipment is able to perform the following processes:

- Weighing;
- Granulation;
- Compression;
- Coating;
- Capsule filling.

After a client's order is inserted on SAP system by Planning and Purchasing sector, an alert is receive by production crew. Based on the alerts received, the responsible for production, in collaboration with PGP director and packaging responsible, will schedule the fulfilment of client's order.

After the production phase is over, two situations may occur: Bluepharma's is responsible for final packaging, or final packaging is not to be performed by Bluepharma.
As I observed, when Bluepharma is not responsible for final packaging, the finished product is stored in jerrycans and sent to warehouse. If Bluepharma is responsible for final packaging, finished product is sent packaging area.

During this training session, I had the opportunity to observe packaging processes applied in Bluepharma. Bluepharma's packaging equipment includes automatic machinery able to fill several types of blisters with tablets or capsules. The responsible for packaging, as the production responsible, has to schedule packaging activities. This will allow packaging finished product almost immediately it is received.
After consulting SAP system, the responsible orders the packaging crew to prepare the machinery in accordance with product specifications. As I observed, this is a very consuming process and sometimes an eight hour shift may be needed to clean and prepare the machinery.
After the finished products is packaged an entry is created on SAP system, and the product is sent to warehouse.

With this experience I got a better look on the steps needed to fulfill an order from a client. Regarding production and packaging steps, I observed that these steps involves several people, from department directors to machinery operators. A high level of coordination between all collaborators involved is needed in order to avoid delays in the processes.

2.1.5 Quality Control

In a one-day training session in Quality Control department, I had the opportunity to follow the activities performed within the scope of this department. I learned that Quality Control department is responsible for analysing every raw-material (active pharmaceutical ingredients, excipients and packaging materials), bulk or finish product that arrives and every bulk or finish product before it is sent to costumers.

I followed a member of Quality Control department during a sampling process for a product prior to its release. The procedure started with an alert received in Quality Control department through SAP system. After the identification of the jerrycans containing the product, I observed how the product was transferred to a room with controlled environment. In this room, an entry in SAP system was made recording the start of the procedure. After that, the jerrycans were open in a specific way, in order to avoid contamination of the tablets. Next, visual checking of the tablets was performed in all jerrycans. A sampling of a few tablets from four jerrycans was performed. The jerrycans were sampling was performed were chosen based on the phase of production the tablets were produced. After completing the sampling procedure, the jerrycans were closed and retrieved from the room.

The samples collected from the jerrycans were sent to Quality Control department laboratory in order to perform analytical and microbiological testing.

Microbiological testing is also a responsibility of Quality Control department department. During my training session in Quality Control department I observe how microbiology testing is performed in Bluepharma.

This visit allowed me to understand how quality control of products in Bluepharma is performed. I observe that there are many laboratory tests that need to be conducted in order to ensure that a product has high levels of quality prior to its release.

Regarding department's equipment, I observed that many times the equipment is shared were other departments, such as Research and Development department. This is a way to maximize the use of the equipment. However, if the activities of the different departments are not coordinated, delays in the processes may occur, which could have impact on company's commitments to its clients and/or partners.

2.1.6 Product Quality & Compliance

Product Quality & Compliance (PQ&C) department is responsible for verifying products compliance with internal and/or costumers standards. A Qualified

Person is responsible for PQ&C management. This Qualified Person is also responsible for batch release in Bluepharma.
During my training session in PQ&C, I learned what activities are developed within the scope of this department. Those activities include: change control generation for equipment specification, equipment calibration/qualification-related activities, management of medicinal product technical documentation, review of documentation related to product production and packaging, Product Quality Reviews, product quality complain management and several other activities.

As referred, the Qualified Person is responsible for batch release; this means that Qualified Person confirms the compliance of the product with technical specifications. Through verifying documentation from Production, Packaging and Quality Control department, PQ&C produce a document known as Certificate of Release. If no non-conformities were found, our Qualified Person approves the Certificate of Release and the product is released.

Before this training session I had no idea the quantity of documentation that is needed to prove that a product is compliant with technical specifications. During this training session I understand that this department needs to be in constant communication with several other departments, since data necessary for product's quality review is originated form several departments. Also, several documentations produced by this department are necessary to complete numerous tasks on other department.

2.1.7 Quality Management

Bluepharma's Quality Management department encompasses the following major responsabilities:

- Work and Environmental safety;
- Site Master File management;
- Bluepharma's Quality Manual management;
- Audit managment;
- Certificate emission (e.g. Halal certificates);

- Management of Bluepharma's internal documentation.
- Supplier qualification;
- Collaborators training management.

During training session in this department it got the opportunity to understand how this department is structured and how the tasks above listed are performed.

Regarding the management of Bluepharma's internal documentation I observed that this is made using the software Ennov®. This software allows distributing documentation in two different levels:

- Standard Operation Procedures;
- Forms.

Although is responsibility of each department to maintain their documentation up-to-date, it is Quality Management department responsibility to code them on Ennov® and them distribute the documentation to all relevant parties.

Several valuable learnings were acquired with this training session. First, I learned that this department is responsible for several tasks with the aim to confirm the high quality of Bluepharma's internal documentation. With this training session, I obtained a deeper knowledge on how Bluepharma's internal documentation is managed and keep up-to-date. Also, I learned how to use the Ennov® software, which was very important for my daily activities since I have to access to several procedures when performing my tasks.

During this session, I observed how Bluepharma's complies with its commitment with environmental responsibility, through activities such as pharmaceutical residue processing. I also learned how Quality Management department manages to comply with health and training requirements of Bluepharma's collaborators.

At the end of this session I concluded that although this is not a very crowded department, Quality Management department encompasses a high variety of activities. These activities also have a central role on the recognition of the quality of Bluepharma's services.

2.2 Pharmacovigilance Activities performed

Pharmacovigilance field presents a significant set of activities that need to be fulfilled in order to ensure the safe use of medicinal products and ultimately allowing MAHs to maintain their MAs. For some activities, as I will present, generic medicines have their pharmacovigilance responsibilities streamline, in line with risk proportionality rule. In the following section, I will describe several pharmacovigilance activities in which I was involved during my internship. Since Bluepharma only has generic medicine MAs, some of the presented activities will be adapted to generics reality.

2.2.1 Pharmacovigilance System

In a way that a MAH can fulfil its pharmacovigilance obligations, the MAH should operate and manage a Pharmacovigilance System, maintaining it always up-to-date. In accordance with Article 104(3) of Directive 2001/83/EC, this Pharmacovigilance System should (5, 27):

- Have permanently and continuously at his disposal an appropriately EU-QPPV;
- Maintain and make available on request a Pharmacovigilance System Master File (PhSMF);
- Operate a risk management system for each medicinal product;
- Monitor the outcome of risk minimisation measures;
- Update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

The EU-QPPV, the contact point for all pharmacovigilance matters, has the main role of managing company's pharmacovigilance system. In accordance with current pharmacovigilance legislation, MAHs should have a written document detailing all the activities performed within the scope of pharmacovigilance inside the company. This document is known as Pharmacovigilance System Master File (PhSMF) (5, 27, 28).

Like any other MAH, Bluepharma as a PhSMF implemented. This PhSMF describes the pharmacovigilance system for Bluepharma and Bluepharma Genéricos.

On this section I will explain the concept of PhSMF location and I will describe the document's structure. As any other system, Bluepharma's pharmacovigilance system has to be continuously monitored. Therefore, I will end this section describing how the performance of this system is evaluated.

Location

Current guidelines suggest that PhSMF should be located at the site where main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates. This place shall ensure that EU-QPPV has a permanent access to it (28, 29).

Bluepharma's pharmacovigilance activities are performed in Bluepharma's building. Therefore, in compliance with authorities' recommendations, Bluepharma's PhSMF is located in Bluepharma's building.

Structure of PhSMF

PhSMF is a complex document. Due to the distinct nature of PhSMF sections, this document should include two distinct parts: primary topic section and annexes. No template for PhSMF content had been provided by authorities. However, some guidance regarding its structure is provided on Article 2 of Commission Implementing Regulation No 520/2012 and on Module II of GVPs (28, 29).

The primary topic section should contain information that is fundamental to the description of pharmacovigilance system. In accordance with Article 2 of Commission Implementing Regulation No 520/2012 this should contain (29):

- Information regarding EU-QPPV;
- Description of MAH organizational structure;
- Sources of safety data;
- Computerised systems and databases;

- Pharmacovigilance processes;
- Description how data is handled during pharmacovigilance activities;
- Pharmacovigilance system performance;
- Quality system;
- Description of subcontracted services.

On the other hand annexes should contain a detailed description regarding of pharmacovigilance activities. Annexes includes mainly two types of information: one encompassing more static information (such as certificates, declarations…) and the other encompassing more mutable information (such as performance indicators, product lists…). Based on authorities' recommendations nine annexes shall be contained in PhSMF (28, 29):

- Annex A – EU-QPPV related information (- should include a list of delegated tasks, *Curriculum Vitae*;
- Annex B – The Organisational Structure of the MAH – should list exiting contracts;
- Annex C – Sources of safety data – a list describing the sources of safety data;
- Annex D – Computerised systems and Databases – section where computerized systems used in the pharmacovigilance system, if any;
- Annex E – Pharmacovigilance Process, and written procedures – list of procedures used in pharmacovigilance activities;
- Annex F – Pharmacovigilance System Performance – list of indicators used to assess system and current results;
- Annex G – Quality System – list of audits scheduled, conducted and/or completed;
- Annex H – Products – list of products that under the scope of the pharmacovigilance system;
- Annex I – Document and Record Control – logbook listing the changes that occurred in the PhSMF annexes.

By the nature of the mutable information contained in annexes, it would be impracticable to track all the changes performed in a PhSMF. Therefore, all changes performed in annexes are recorded in the logbook present in Annex I.

Assessment of the Pharmacovigilance System

In order comply with Article 2 of Commission Implementing Regulation No. 520/2012 MAHs should include in their PhSMF a description of process used for monitoring the performance of the pharmacovigilance system (29). On PhSMF section "Pharmacovigilance system performance" the MAH should at least describe (28):

- The evaluation system used to assess the correct reporting of ICSRs;
- The metrics used to monitor the quality of submissions and performance of pharmacovigilance;
- How PSUR submission to authorities is monitored;
- How variation submissions are monitored;
- How Risk Management Plans commitments, if any, are monitored;
- Other metrics used to evaluate the performance of the system.

In accordance with Article 9 of the same regulation, MAHs may use performance indicators to evaluate the performance of the system (29). In Bluepharma's PhSMF a list of performance indicators is present on Annex F. This list is composed by the following indicators:

Table 3 – Performance Indicators used in Bluepharma pharmacovigilance system

Type of Performance Indicator	Performance Indicator
ADR/AE input management	• Rate (%) of received ADR/AE per source • Average time needed for validation decision
Literature Research	• Rate (%) of literature researches • Rate (%) of processed literature research cases • Rate (%) of valid ADR originated from literature research
Management of valid ADR	• Rate (%) of valid ADR/AE per source • Rate (%) of valid ADR occurred in EU • Rate (%) serious ADR • Rate (%) non-serious ADR • Rate (%) of compliance on notification processes • Rate (%) of compliance on notification deadlines
PSUR	• Rate (%) of compliance on PSUR submissions

Type of Performance Indicator	Performance Indicator
	• Rate (%) of compliance on PSUR submission deadlines • Rate (%) of synchronized PSUR • Average time needed for PSUR submission upon the Data Lock Point (± Standard Deviation)
Risk Management Plan (RMP)	• Rate (%) of medicinal products with RMP • Rate (%) of RMP with "Risk minimization measures" • Rate (%) of compliance on RMP updates • Rate (%) of compliance on RMP updates deadlines
Safety variations	• Rate (%) of safety variations • Rate (%) of compliance on safety variations submission deadlines
Signal detection	• Rate (%) of signal detections
Security measures	• Number of security measures per year • Number of DHCP per year

During my internship, one of my tasks was to create in a three-month period basis a report evaluating Bluepharma's Pharmacovigilance system in the previous three-months, using the above mentioned indicators. After extracting data from relevant internal data-loggers and using an already established template, I elaborated a report presenting the results of the system performance in the concerned period. This report is then reviewed and signed by Bluepharma's EU-QPPV. The signed version of the report is substitutes the previous version present on Annex F of PhSMF .

This was a very rewarding experience for me. Doing this I had the chance to participate in the evaluation of Bluepharma's pharmacovigilance system. With this activity I had the opportunity to observe which activities are performed in Bluepharma related to pharmacovigilance.

Another important finding for me is that for several activities the compliance rate must be 100%. If the value obtained is under this value, this mean that Bluepharma did not comply with its pharmacovigilance activities.

In the course of time MAHs responsibilities might change. This may lead to the elaboration of new indicators in order to monitor the compliance with a new specific responsibility. Or, in other hand, an indicator may become obsolete and be withdrawn from the assessment.

By analysing the data I get the opportunity to be involved in Bluepharma's pharmacovigilance system management. The information extracted from performance indicators contributes for the continuous improvement of the system. Consequently, systems performance is improved.

2.2.2 Changes in Legislation Monitoring

As already proved, pharmacovigilance is a field with a very strong regulatory basis. Through regulations, directives or simply through guidance documents several entities publish documents that are relevant for the well conducting of pharmacovigilance activities. These entities might provide national, regional or even global guidance.

With the development of new technologies or techniques, or even due to specific safety concerns, updates in regulatory documents provided by these entities might be published and have impact on pharmacovigilance activities. Therefore, it should be a priority for MAHs to develop and maintain a system allowing them to successfully monitor the publishing of such documents.

Also, through a successful monitoring system of changes in pharmacovigilance legislation it will be possible to comply with Pharmacovigilance System quality present in Module I objective a: *"Complying with the legal requirements for pharmacovigilance tasks and responsibilities"* (5, p5) (30).

Bluepharma, as referred previously, has an Investigation, Development and Innovation certification. One requirement necessary to maintain this certification is to prove that knowledge that arose from external sources, this is knowledge from entities outside Bluepharma and relevant for the internal activities, is not lost. Therefore, Bluepharma implemented a software system (InnovWay®) which allows the recording of vigilances that arose from the monitored entities and distribute those vigilances to the relevant parties inside Bluepharma.

Bluepharma is an EU based company with MAs are mostly approved in Portugal. Therefore, an exhaustive monitoring of the entities that might provide guidance for approved medicinal products in Portugal should be made. Those entities were monitored on a weekly basis.

On below, I will list which entities are monitored and describe in detail how they are monitored. Also, I will describe how vigilances are created in order to comply with Investigation, Development and Innovation certification requirements.

Portuguese Entities

Being Bluepharma's MAs present mostly in Portugal, the entities that are periodically monitored are those that might influence the pharmacovigilance activities performed in Portugal. It should also be referred that there is no official list of such entities, thus MAHs should act proactively finding those institutions.

Locally entities, this is Portuguese entities; that are monitored are the following ones:

- Portuguese Assembly;
- Diário da República;
- Infarmed, IP.

Portuguese Assembly

Portuguese Assembly is one of Portuguese sovereignty institutions. It is responsible for the development and approval of Portuguese laws. Also, since EU directives need to be incorporated into national legislation ("transposition"), the monitoring of Portuguese Assembly publications is crucial in order to know when the rules present in a new EU directive are applicable to Bluepharma's MAs (31).

In Bluepharma, this entity is regularly monitored by consulting its website and by monitoring daily publications of *Diário da República*. By monitoring On Assembly's website it is possible to follow the developments on a new legislative act. For that, two tools present on the website are consulted:

- *Últimas Iniciativas Entradas* – where new legislative acts to be discussed by Portuguese parliamentarians are listed (32);

- *Últimos Textos Aprovados* – where legislative acts approved by Portuguese parliamentarians are listed (33).

The texts listed on *Últimos Textos Aprovados* need yet to be published on *Diário da República* in order to be considered official documents. Therefore, in Bluepharma, *Diário da República*'s website is also regularly monitored in order to known when new legislative acts applicable in Portugal came into force. This comprises the monitoring of both series that are updated on a daily basis (34):

- Series A – comprising laws and decree-laws that were published;
- Series B – comprising despatches, ordinances and other relevant official documents.

Infarmed, IP

Infarmed, IP is the Portuguese Competent Authority responsible for regulation and market surveillance of medicinal products, medical devices, homeopathic products and cosmetics. Therefore, it is essential be up-to-date with recommendations provided by this institution. Since laws are published by Portuguese Assembly, monitoring of Infarmed is intended to obtain further guidance from the laws published by Portuguese Assembly.

The monitoring of this institution is made by consulting recent updates that were published in its website. For this, the tool present in the website "*Mais Novidades*" is consulted. However, this tool does not provide all the updates that have occurred in the pharmacovigilance field. Thus, the section of Infarmed's website intended to provide guidance for pharmacovigilance activities is also periodically monitored.

Regional Entities

Regional entities, this is entities that act centrally in EU; that are monitored are:

- European Medicines Agency;
- Heads of Medicines Agencies;
- European Commission;
- European Parliament;

- European Consilium;
- Official Journal of the European Union.

European Commission, Parliament and Counsillium

A legislative act in European Union level only becomes official after being published on *Official Journal of the European Union*. Therefore, as happens in for *Diário da República,* this journal is regularly monitored in order to known new legislative acts developed by European Union legislative institutions that might impact Bluepharma's pharmacovigilance activities (35).
However, MAHs should not be caught off guard when a new legislative act gets into force. Therefore, accompanying the discussions related to pharmacovigilance between EU legislative institutions is essential.

Before showing how those institutions are monitored, I will summarize how an ordinary legislative act at EU level is conducted. On normal circumstances this process starts with a proposal for a legislative act being drawn up by European Commission. This proposal is sent to European Parliament where it is discussed and voted by European parliamentarians. If the proposal is adopted by the parliamentarians it is then sent to European Consilium. If adopted by the consilium the proposal is then published on *Official Journal of the European Union*, becoming this way an official document (35).

Those proposals are monitored mainly through consultation of European Parliament's database *Legislative Observatory*. By consulting this database it is possible for users to monitor the phase in which the document is being discussed and access to the most recent version of the document that is under discussion (36). However, in order to access other relevant documentation related to the legislative act that is being discussed, the official website of each institution is also monitored.

European Medicines Agency

As already referred on sections before, EMA is the EU institution that acts at a central level that is responsible for regulation, supervision and coordination of

pharmacovigilance activities (5). Therefore, this is another centrally entity acting that is monitored.

Through monitoring its website tool *What's New?* it is possible for users to get access to all updates that have occurred in EMA's website. This way MAHs get access to guidance documents that may affect its pharmacovigilance activities.

Heads of Medicines Agencies

The Heads of Medicines Agencies (HMA) is a network of the Heads of the National Competent Authorities whose organisations are responsible for the regulation of Medicinal Products for human and veterinary use in the EEA. Through its working groups HMA provide to MAHs several guidance documents that should be used when performing its activities (37).

Since for centrally approved medicines these activities are already covered by EMA, the guidance documents provided by HMA are mainly intended for MAs granted by national procedures (i.e Mutual Recognition Procedure, Decentralised Procedure or purely national) (37).

In Bluepharma, the monitoring of this entity is performed by consulting the tool present in HMA's website *What's new history* that allows users to consult every updates that occurred in the HMA website in the previous six months (38).

Global Entities

Global entities that are monitored are:

- International Conference on Harmonisation;
- Council for International Organizations of Medical Sciences.

International Conference on Harmonisation

ICH is an entity created in 1990 that brings together the regulatory requirements of the three major markets for medicinal products: EU, Japan and the USA. It is ICH mission of harmonize the technical requirements for medicinal product registration. Therefore, MAHs should be aware of guidelines published, or updated by ICH. To do this, in Bluepharma ICH's website was regularly monitored in order to get access to such guidelines.

Council for International Organizations of Medical Sciences

CIOMS is another globally acting entity that provides relevant guidance for pharmacovigilance activities. As already referred before, this is an entity associated with WHO created in 1949 (see 1.3.2). In Blupharma, this entity was regularly monitored by consulting its website (39).

Recording of vigilances

During the process of monitoring an entity, documents with potential to affect pharmacovigilance activities might be detected. A reference for those documents is created on an internal data-logger for further assessment.

After being evaluated, if a document is considered as being susceptible to affect pharmacovigilance activities in Bluepharma, an entry is also created on InnovWay® software. The entry created in this software will contain an assessment of the possible outcomes for pharmacovigilance activities. The entry created is then sent as an e-mail alert for all relevant Bluepharma's collaborator.

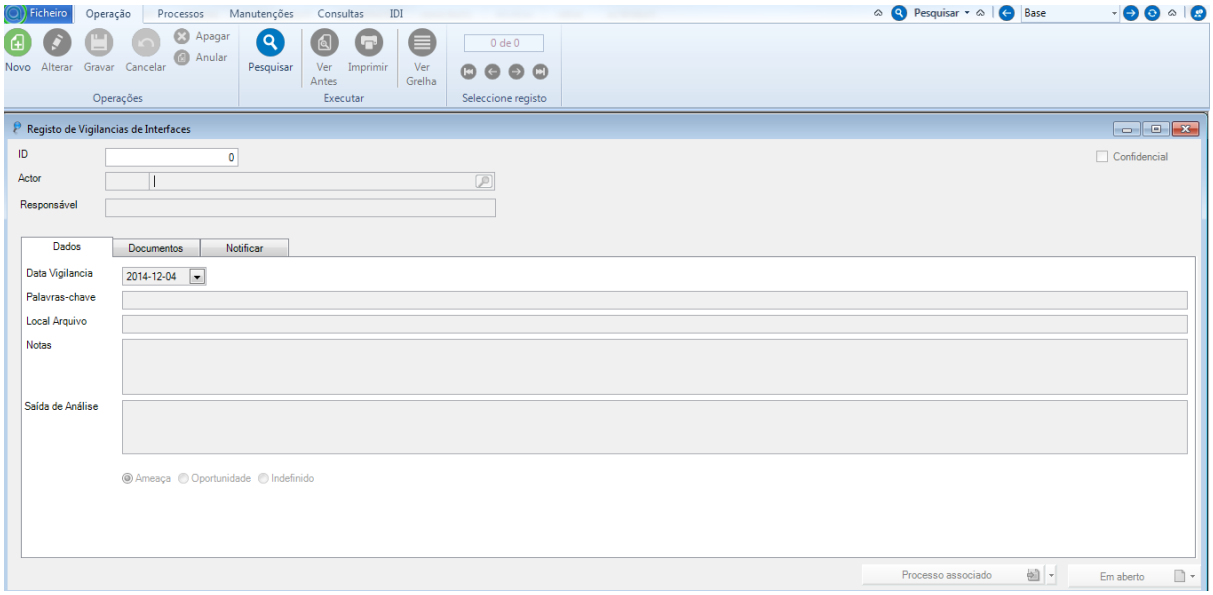

Figure 6 – InnovWay® vigilance record

In conclusion, this is the process performed on Bluepharma to accomplish its objectives to comply with legal requirements and the internal Investigation, Development and Innovation objectives. This task allowed me to understand

that there are several institutions providing to MAHs guidance documents on how to conduct their activities. These institutions can, in certain instances, not only provide guidance for locally based MAHs but guidance in a worldwide scale.

2.2.3 Risk Management System

The use of a medicinal product is not exempted of risks, either identified or not. It is required for MAHs to maintain internal systems that allow the tracking of those risks. These systems are called Risk Management Systems.

Therefore, a Risk Management System represents all the *"activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions*" (2001, p14), as stated on Article 1 of Directive 2001/83/EC (5).

The primary objective of the implementation of these systems is to ensure that the benefits of using a medicinal product outweigh the risks. As referred in GVPs Module V, this can be accomplished by increasing the benefits of using the medicinal product or by decreasing its risks, although Risk Management Systems are mainly designed to mitigate the risks (40).

The cycle of risk mitigation, also known as risk management cycle (see Figure 7), begins with the collection of safety data related to the medicinal product. After the analysis of those data a new safety concern (risk) related to the medicine use can be detected. This risk is then evaluated in order to determine if it has impact on risk-benefit balance. After the analysis, and if necessary, one or several measures can be defined as appropriate to deal with the risk identified. The most suitable are then applied, whose impact will be assessed posteriorly (40).

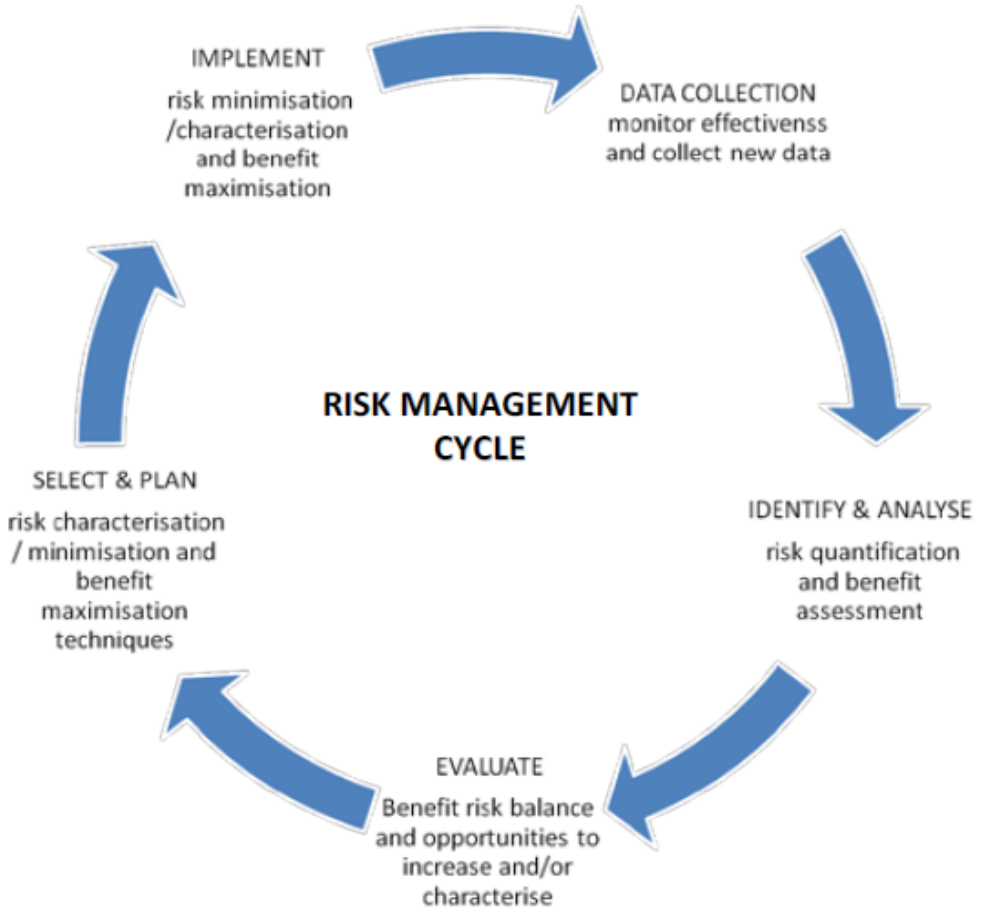

Figure 7 – The risk management cycle (40)

The measures referred to be present on a Risk Management System are described on a document called RMP. On the following pages I will describe how a RMP is planned, developed and submitted to authorities.

RMP planning

When I arrived to Bluepharma, competent authorities were implementing new requirements related to the submission of RMPs and MAHs needed to comply with this new requirements. These requirements derived from the transposition to national legislation of the new requirements present on Directive No. 2010/84/EC, amending Directive No. 2001/83/EC.

MAHs were required the submission of the following documents:

- Risk Management Plans;
- Summary of Pharmacovigilance System.

Regarding the submission of RMPs, following the publication of Infarmed's guidance, MAHs were required to submit an RMP for their products whose MAA was made after 21 July 2012 and do not present an RMP at the time. This had to be fulfilled until 27 December 2013. This also means that new MAA should present a RMP in section 1.8.2 of CTD (41). I receive the assignment to list all Bluepharma's products that needed an RMP to be submitted.

Summary of Pharmacovigilance System is a regulatory document that should be included in CTD's sub-module 1.8.1 upon MAA (41). This document is a summary of applicant's Pharmacovigilance System and should at least include the following (40):

- Identification of EU-QPPV, including contact details;
- Statement by applicant that it possesses all the necessary resources to fulfil its pharmacovigilance responsabilities;
- Reference to PhSMF location.

In contrast with the need for submission of an RMP, the Summary of Pharmacovigilance System has to be submitted for all MAH's products upon product renewal or until 21 July 2015 through a variation, whichever first (41).
In parallel with the assignment to determine which Bluepharma's products needed the submission of a RMP, I also listed Bluepharma's products that could have their Summary of Pharmacovigilance System submitted upon renewal or through a variation.

<u>RMP Development</u>

After consult all Bluepharma's dossiers it was concluded that a RMP had to be submitted for one product. I had the chance to develop this RMP. During this activity I use the previously prepared Bluepharma's template for RMPs. This template is in accordance with harmonized format of RMPs for applicants of generics applications should use. The development of this harmonized was intended to facilitate the RMP production by MAHs and its evaluation by the authorities (29). RMP structure is expected to have the following modules (40):

- 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
- Part IV: Plans for post-authorisation efficacy studies
- Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)
- Part VI: Summary of the risk management plan
- Part VII: Annexes

Due to the principle of proportionality of risks, which states that Risk Management Systems should be proportionate to the potential and identified risks, the structure of RMPs for generic applications was streamlined (5, 40). Therefore, as present on GVP Module V, RMP sub-modules SI to SVII may be omitted. Also Parts III and IV might be omitted if no additional pharmacovigilance or efficacy studies were imposed to the reference product (40).

RMP production was based on the safety concerns identified for the medicinal product presented in reference product's SmPC. Reference information for generics should be in accordance with its innovative's reference information. Therefore, the risks identified for reference medicinal product should be the same for the generic medicinal product. In this sense, it is recommended the use of reference product's SmPC for describing the safety concerns identified during generic medicinal product applications (18, 40).

Submission

Regarding the submission of Summary of Pharmacovigilance System Infarmed requested the submission of variations for products needing a Summary of Pharmacovigilance System. However, an exception was created for products already in process of renewal at Infarmed. For those products Infarmed requested the submission of Summary of Pharmacovigilance System through e-mail for renovacao.nacional@infarmed.pt, this way saving MAHs of paying the costs of a variation (41).

The previously referred list for products' Summary of Pharmacovigilance System also contained this variable. Through it I extracted a list of products that where already under renewal process. The list was then sent to the referred e-mail with a cover letter requesting the inclusion of Bluepharma's Summary of Pharmacovigilance System in the process.

As referred before, a variation had to be submitted for the product whose RMP was needed. I got the change to understand how a variation is submitted. This variation was submitted as any other variation using Infarmed's online platform for submission of variations (SMUH-ALTER) (42). In terms of variation classification the rules present on European Commission guidelines for variation classification were used. Based on those guidelines a Type II variation classified as "C.I.11 - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan" was submitted to Infarmed (43).

In conclusion, the assignments presented on this section allowed me to obtain a better understanding of an RMP structure and content. Being Bluepharma's products generics, this activity allowed me to understand the differences between a RMP for an innovative product and for a generic medicinal product. Since the risks identified in the RMP were the risks presented on innovative's SmPC, this activity made me understand the importance of maintaining generic product information in line with reference product's information. .

This activity also allowed me to be introduced into the rules governing the submission of variations. With the task involving Bluepharma's Summary of Pharmacovigilance System I obtain a better knowledge about the structure and

content of this type of documents and the situations where they have to be submitted.

2.2.4 Medical and Sicentific Literature Monitoring

Following the Regulation (EC) Nº 726/2004 it was determined that a close monitoring of possible ADRs arousing from reports published in medical and scientific journals was needed. Therefore, in accordance with the Article 27 of this regulation: *"the Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish the list of active substances being monitored and the medical literature subject to this monitoring"* (3, p30) (18).

However, due to budget constraints, a draft list with active substances to be monitored by the Agency was only published in the beginning of 2014. In accordance with information provided by the Agency, the monitoring of scientific and medical literature for reports of suspected adverse reactions by the agency is expected to start in 2015 (44).

Following the publication 2012 pharmacovigilance legislation, a series of guidelines aiming to support pharmacovigilance activities and replace Volume 9A of Eudralex were launched. In Module VI (concerning the management and reporting of ADRs) provide guidance how MAHs should maintain a system to monitor ADR reports from literature during this transitional period (23, 45).

As stated on GVP Module VI, literature reports are a significant source of safety information related to medicinal products. Therefore, it is expected MAHs to systematically and frequently (at least once per week) to monitor important databases of medical and literature references (such as Pubmed®). Also, local publication in journals non-indexed to those databases should be monitored. Through this procedures it is expected MAHs to become aware of safety concerns at a global and a local level (23).

In this section I will explain in detail how monitoring of medical and scientific literature were performed in Bluepharma. For that purpose I will start to describe how the international database Pubmed® is monitored followed by a description

of the procedure applied to Portuguese non-indexed journals. The information regarding the process of validation of an Individual Case Safety Report (ICSR) will not be discussed in this section. On the section 2.2.5 I will describe this process in detail.

International databases

During my internship at Bluepharma's pharmacovigilance sector one of my time-consuming tasks was the related to weekly systematic review of relevant medical and scientific literature recorded on the international citation database Pubmed® (46). In Bluepharma, it was choose to use this database because it is one the most largest international citation databases, and Pubmed® is one of the most used databases in pharmaceutical industry for bibliographic searches.
Once a week (usually on Monday) an e-mail alert (for each product) is receive on pharmacovigilance system e-mail address with the citations recorded on Pubmed® during the previous week. This is possible using the *My NCBI* tool (see Figure 8) (47).

The searches performed on Pubmed® were performed individually for each active substance as suggested by GVP guidelines. Searches performed using medicinal product name and active substance name would only give MAHs better recalls rates. However, to obtain better balances in the searches, this is more precise searches, more complex search algorithms using other search terms should be used (23). In Bluepharma, the search algorithm used had the following terms:

- [Active substance];
- Adverse event;
- Pregnancy
- Overdose
- Medication error
- Off-label use
- Misuse
- Abuse
- Occupational exposure

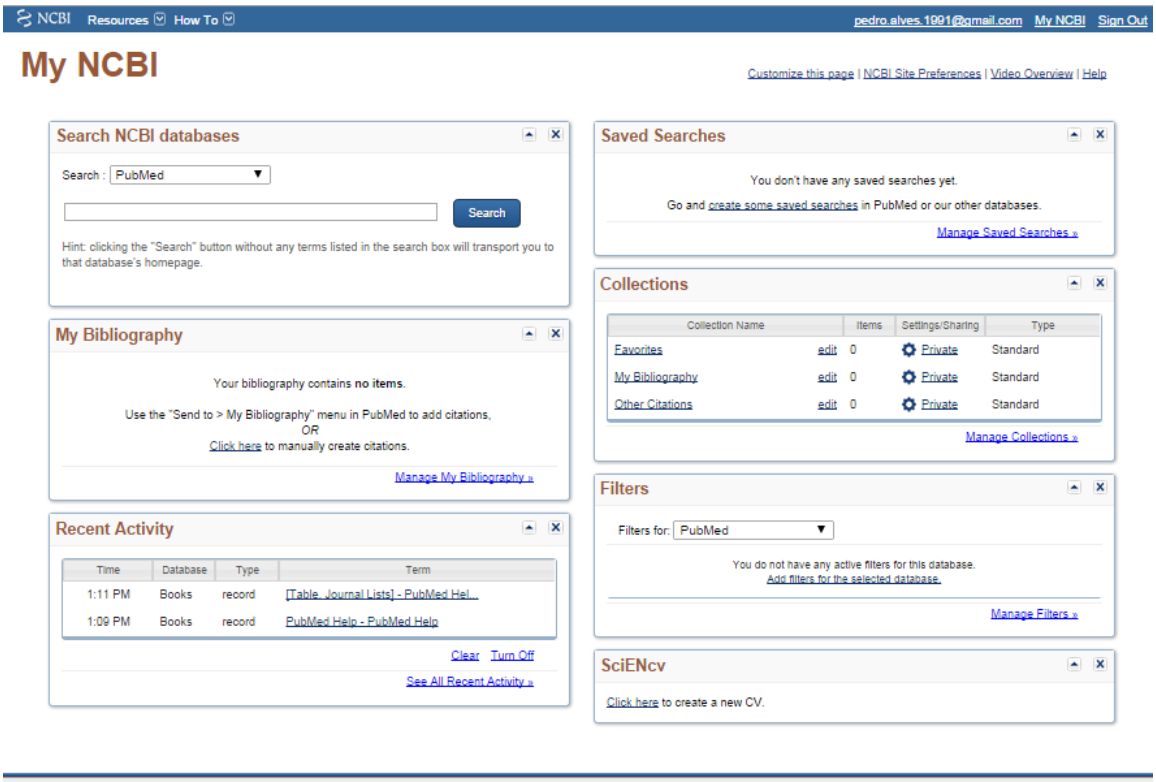

Figure 8 – My NCBI tool

With this search algorithm it was expected to comply with GVP's Module VI recommendations (23). When a new active substance is included on Bluepharma's portfolio, a new entry for it is created on *My NCBI* and thereafter an e-mail alert for is receive every week.

Non-indexed journals and abstracts from meetings

Since international databases have a limited reach in terms of local publications, it is expected MAHs to have procedures in place to monitor medical and scientific publications in local journals where medicinal products have a marketing authorization (23).

When I started reviewing medical and scientific literature in Bluepharma those procedures where still under development. Due to my previous experience in academic projects I was involved in their development. During that process I listed Portuguese journals (indexed and non-indexed journals) that were published in Portugal at that time. Based on the criteria of medical specialty discussed in each journal, a final list with seven journals related to the medical

specialty of Bluepharma portfolio was obtained. Therefore, the journals that I started to review were the following:

- Revista de Fatores de Risco;
- Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo;
- Revista Portuguesa de Ortopedia e Traumatologia;
- Sinapse;
- GE - Jornal Português de Gastrenterologia;
- Revista Portuguesa de Doenças Infecciosas;
- Revista Portuguesa de Hipertensão e Risco Cardiovascular.

However, due to the fact that most relevant meeting abstracts are not added to Pubmed® it was decide to monitor some Portuguese journals indexed to Pubmed®, in order to assess special publications with meeting abstracts. This was decided based on the fact that most relevant meeting abstract books are published on those journals. Thus, the journals whose special editions were monitored were the following:

- Revista Portuguesa de Cardiologia;
- Acta Médica Portuguesa;
- Acta Reumatológica Portuguesa.

In conclusion, this is the process performed in Bluepharma for reviewing relevant medical and scientific literature. Through being part of it I understand the importance of doing it to become aware of new safety concerns. It was also changeling to be involved in the development of procedures to monitor local publications, due to its specificities.

2.2.5 Individual Case Safety Report

When consuming a medicinal product a patient may suffer adverse events possibly related to the medicinal product. These suspected adverse reactions can be communicated to MAHs (23):

- Directly by the patient;
- By a third party, such as pharmacists or other health care professionals;
- By a Competent Authority notification.

The information collected during these reports can be organized on documents with specific formats (e.g. CIOMS I form). These documents are specific to a reaction (or several) that happens to a patient in a specific moment. They are organized in a way that is possible to identify: the reporter(s), patient, reaction(s) and medicinal products suspected of causing the reaction (23).

In accordance with Article 107 of Directive 2001/83/EC, MAHs should have a system to allow them to record all suspected adverse reactions that may be aware of, independently the reporter or the country of origin. However, as we will see next, not all the reports presented in this system need to be submitted to competent authorities. Also, the requirements for reporting will depend on the status of the medicinal product; this is if it already has a MA or if it is still an experimental product (5).

With 2010 legislation the reporting system has also been updated. Due to improvements in Eudravigilance platform MAHs are now required to submit all reports of suspected adverse reactions electronically (independently of the type of MA procedure) (5, 23).

In this section I will describe how a report of a suspected adverse reaction possibly related to a Bluepharma's product is processed since it is received until is submitted to the Competent Authorities.

Collection of reports

Collection of AE reports can occur either from solicited reports, this is reports originated on organized data collection systems (e.g. clinical trials, non-interventional studies), or from unsolicited sources, this is reports describing the occurrence of an AE on a specific patient and on a specific moment and not originated on organized systems of data collection. For purposes of this report, only AE reports derived for unsolicited sources are relevant (23).

In accordance GVP module VI, there are four source types of unsolicited reports (23):

1. **Spontaneous reports** – communication by a healthcare professional, or consumer to a competent authority, marketing authorisation holder or other organisation (e.g. Regional Pharmacovigilance Centre) that describes one or more suspected adverse reactions in a patient who was

given one or more medicinal products. In Bluepharma, sales representatives may also be a source of spontaneous report, if a suspected ADR to a Bluepharma product is reported to them during their visits;

2. **Literature reports** – report of suspected adverse reactions from the scientific and medical literature;
3. **AE reports from internet or digital media** – reports of suspected ADRs from digital media considered owned by the MAH;
4. Reports from other sources

During my internship in Bluepharma I learned what procedures are in place to receive/monitor suspected ADR reports from those sources.

Validation of reports

In the tasks that were allocated to me during my internship, validation of reports from literature reports was one the most time consuming. Those reports arose during the literature monitoring described on section 2.2.4. By analyzing the literature article I assess if it had all the validation criteria, and therefore qualified for reporting. These criteria are:

- An identifiable reporter (name, initials or address);
- An identifiable patient (initials, patient identification number, date of birth, age, age group or gender);
- One or more suspected substance/medicinal product;
- One or more suspected adverse reaction.

Follow-up of reports

Due to the fact that sometimes the information presented in suspected ADR reports may be incomplete, GVP module VI suggests MAHs to contact reporter(s) for further information regarding the ADR report. This is particularly important for monitoring events of special interest: prospective reports of pregnancy, cases notifying the death of a patient, cases reporting new risks or changes in the known risks.

In Bluepharma there are procedures in place in order to contact reporters when further details about a suspected ADR are needed. Those contacts may be performed through e-mail or telephone, accordingly with the contact available. During my internship I had the chance to observe how follow-up contacts are conducted and information retrieved from those contacts is recorded.

Validated case assessment

After case validation it is necessary to verify if the case will be effectively reported, and if so what information should be contained in the report. This is done in a step-by-step process by evaluating (48):

1. Causality assessment.
2. Relevance of the experience (e.g. expectedness, seriousness…);
3. Codification of case-report;
4. Quality of documentation (e.g. completeness of data, initial report vs follow-up report);

During this evaluation (especially during the causality assessment) the following characteristics of the AE are taken into consideration (49):

- Temporal relationship;
- Outcomes of treatment suspension and/or re-challenge (if available);
- Reaction profile:
    - Clinical and/or laboratorial manifestations;
    - Severity and intensity;
    - Frequency of reaction;
    - Possible mechanism of action;
    - Pre-disposing factors (e.g. basal diseases, concomitant medication…)
- Pharmacological plausibility;
- Supplementary data.

In Bluepharma, two methods of causality assessment are used:

- Naranjo's scale;
- Global Introspection.

Naranjo's scale is performed by pharmacovigilance operators after a suspected ADR related to a Bluepharma's product is validated. This method is based on a score system obtained from the evaluation of the suspected ADR in relation to a series of specific question (see Table 4). Based on the score obtained the causality of the reaction may be classified into (25):

- Definite (score above 9);
- Probable (score between 5 and 8);
- Possible (score between 1 and 4);
- Doubtful (equal to 0).

Table 4 – Naranjo's scale (25)

Question	Yes	No	NA	Score
1. Are there previous *conclusive* reports?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when drug was discontinued or specific antagonist was administered?	+1	0	0	
4. Reaction was more severe with increased dose or less severe with decreased dose?	+1	0	0	
5. Did the reaction appear when the drug was readministered?	+2	-1	0	
6. Are there other nondrug causes for the adverse event?	-1	+2	0	
7. Did the reaction appear when a placebo was given?	-1	+1	0	
8. Was a toxic serum concentration noted?	+1	0	0	
9. Does patient have a history of similar reaction with drug or drug class?	+1	0	0	
10. Adverse event confirmed by any objective evidence?	+1	0	0	
			Total Score	

Global Introspection is the algorithm followed by Pharmacovigilance sector associate physician to classify suspected ADR. This method involves clinical judgment about the suspected ADR. Based on this method, a suspected ADR can be classified into:

- Certain;

- Probable;
- Possible;
- Unlikely;
- Conditional;
- Unassessable.

During my internship, I participated in the evaluation of the suspected ADR report, including the assessment using the Naranjo's scale. Product's SmPC was used as reference information during this process. Additionally, with the information extracted from the report I filled the appropriate fields on an internal data-logger and a CIOMS I form, as required on internal procedures.

Reporting of ICSRs

During my internship in Bluepharma I participated in the submission of suspected ADR reports to competent authorities. In accordance with reporting requirements present on Article 107a (4) of Directive 2001/83/EC (as emended by Directive 2010/84/EC), MAHs shall report in no more than fifteen days after receiving the ADR report for serious ADRs and no more than ninety days for non-serious reactions (5).

However, during transitional period, some competent authorities do not require the submission of reports of non-serious ADRs. Infarmed is one of those authorities (24).

The ADR reports, as required on Article 172 of Decree-law 176/2006, were reported through EMA's electronic platform Eudravigilance (see Figure 9) (50). In this platform there is a field allowing MAHs to choose which authority will receive the report. After selecting Infarmed and filling the appropriate fields related to the reaction description the report was sent.

Figure 9 – Eudravigivilance plataform

After a message confirming the acceptance of the suspected ADR report by the authorities, a CIOMS I form with the information reported was retrieved from Eudravigilance. A paper copy of the article with a CIOMS I form with the information retrieved from Eudravigilance was then recorded on an appropriate file case in Bluepharma's archive.

With this activity I got the opportunity to obtain experience in the identification, validation and evaluation of suspected ADR reports. I also learned that for causality assessment, clinical judgment is in most cases needed to understand the relation between suspected ADR reports and the suspected medicine. By participating in the submission of suspected ADR reports I get the opportunity to be in contact with Eudravigilance platform.

2.2.6 Periodic Safety Update Reports

Portugal and European Union

As laid down on Directive 2001/83/EC, one of post-marketing obligations of MAHs is the submission to competent authorities of Periodic Safety Update Reports (PSUR). PSURs are documents expected to discuss critically the safety and efficacy profile of a medicinal product taken into account the most up-to-date scientific evidence related to a medicinal product (5).

As present on Article 104 of Directive 2001/83/EC, PSURs should be submitted to competent authorities "*immediately upon request or at least every six months during the first two years following the initial placing on the market and once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request*" (2001, p92). With 2010 pharmacovigilance legislation PSUR submission frequency for products containing some active substance had been levied with the publication of lists with union reference dates and frequency of PSUR submission. The influence of those lists on Bluepharma's products is discussed below (5).

The publication of 2012 pharmacovigilance legislation also had impact on PSUR-related activities. PSUR format had been harmonized in all EU member states, in order to facilitate the exchange of safety information between competent authorities. This new format also enhanced the identification and evaluation of safety concerns present on PSUR (29, 51).
In the following sections I will describe the steps that are related to a PSUR since it is forecasted to be submitted until the MAH receive the outcomes from competent authorities' evaluation.

PSUR forecasted to be submitted

When I started my internship at Bluepharma, PSURs frequency of submission were based on two lists, one from EMA and the other from HMA, which complements each other. Article 107e of Directive 2001/83/EC sets out that PSURs of products containing the same active ingredient but marketed in different member-states should be assessed by Single Assessment procedure; this is, PSURs will be jointly assessed by PRAC or by a member-state appointed by CMDh, depending on which list the product falls. The outcomes of PSUR assessment will be shared among all MAHs with products containing the active substance (5).

It is present on Article 107c of Directive 2001/83/EC that products containing the same active ingredient but marketed in different member-states should have their PSUR submission frequency harmonized in order to make possible the

Single Assessment. To make this possible EMA regularly updates and publishes list of Union reference dates and frequency of submission of PSURs on its website. This is the first list whose publication I had to monitor. After its publication I had to evaluate if any change occur to previous versions that might impact Bluepharma's products PSUR submission (5).

However, not all active substances that are marketed in more than one member-state are in the above mentioned list. During the transitional period and until EMA has the capability the assess PSURs of all products under a national procedures, some active substances were temporarily allocated to a list managed by CMDh: *List of Substances under PSUR Work Sharing Scheme and Other Substances contained in Nationally Authorised Products with Data Lock Point Synchronised* (52). That's the second list that whose publication I had to monitor and evaluate the impact on Bluepharma's pharmacovigilance activities.

Internally, the relevant sections for Bluepharma of both lists were compiled into a data-logger in order to facilitate the identification of PSUR submission frequencies for Bluepharma's products. When changes occur in one of these lists affecting PSUR's frequency of a Bluepharma product this data-logger is updated in accordance with the updated list.

PSUR preparation and submission

During my internship I had the opportunity to participate in the preparation and submission of PSURs. Although many Bluepharma's products have waivers under Articles 10(1) and 10a of Directive 2001/83/EC to the obligation of submitting PSURs, there is still a significant list of Bluepharma's products which requires the submission of PSUR. These waives are defined on the lists referred on the previous section (5).

The content of PSUR should be in accordance with the template present on Annex II of Commission Implementing Regulation No. 520/2012. Guidance regarding on the information that should be inserted in each section is provided on GVP Module VII (29, 51).

I had the opportunity to participate in the preparation and submission of PSURs for Bluepharma's products. In those submissions, requirements presented on EMA guidance document "*National Competent Authorities and European Medicines Agency (EMA) requirements for submission of PSUR during the transitional period*" were followed (53). Meanwhile, this guideline was suppressed by the following HMA guidance document: "*Requirements on Submissions for Periodic safety update reports (PSUR) to National Competent Authorities for products authorised via National Procedures, Mutual Recognition Procedure and Decentralised Procedure*". At the time of the preparation of this report, no PSURs for Bluepharma's products were submitted under these requirements (54).

Taken into account the requirements presented on the supressed guidance, a CD-ROM with a .pdf version of the PSUR and a cover letter in paper were mailed to Portuguese competent authority.

Being the active substance in cause subjected to Single Assessment, the guidance also requested the submission of the PSUR to all PRAC and CHMP members representing the national competent authorities of member-states where the medicinal products were authorised, to the PRAC rapporteur of the procedure, and to EMA. For this, as suggested in the guidance, we use the requirements present on the guidance document "*Dossier requirements for Centrally Authorised Products*". Taken into account the requirements present in that guidance document, a PSUR is eCTD format was submitted to the above mentioned entities (55). This was the first time that a PSUR was by Bluepharma in this format, so it was a learning experience for all pharmacovigilance team.

My tasks related to planning, preparation and submission of PSURs allowed me to get a greater knowledge about EEA legislation that regulates PSURs. By participating in the submission of PSURs in Europe I get the opportunity to observe how documents are submitted in eCTD format, which was a novelty for me. Before this experience I had no idea how many entities must be contacted for PSUR evaluation. Therefore, after this activity I realize that over time PSUR evaluation has the tendency to become more and more centralized process in EEA.

Mozambique

As verified in the previous section for Portugal and the other EU member states, in Mozambique MAHs have the obligation to submit PSURs to competent authorities. This obligation is stated on Article 13 of Ministerial diploma No. 53/2010. In accordance with this article, a MAH must submit a PSUR (56):

- Immediately after authority's solicitation, or;
- Every six months in the first two years after MA approval, yearly in the next two years and every three years thereafter;
- At renewal.

In the following sections I will describe the activities that are related to PSUR planning, preparation and submission in Mozambique since the PSUR is forecasted to be submitted until it is submitted to Mozambican competent authorities.

PSUR planning, preparation and submission

Mozambican authorities provide MAHs with specific guidance regarding the production and submission of PSURs. MAHs can consult those recommendation on Ministerial diploma No. 53/2010 and on specific guidance documents.

In order to have a better management of PSUR submission, the activities related to PSUR submission should be planned. This would allow me to obtain all the necessary documentation before its preparation. In Bluepharma I participated in the creation of an internal data-logger to manage PSUR submission to Mozambique. This data-logger was created based on Article 13 of Ministerial Diploma No. 53/2010 submission requirements. Through this data-logger it was possible a better tracking of PSURs to be submitted to Mozambican competent authority. Also, this data-logger allowed me to obtain data that can be used to evaluate the system regarding the submission of PSURs to Mozambique.

Based on Mozambican guidance for the PSUR production provided to us by a local contact point, I participate also in the elaboration of an internal template for

the production of PSURs. In accordance with Mozambican guidelines a PSUR should contain the following structure (57):

Cover Page

1. Introduction
2. Worldwide status
3. Regulatory actions or actions taken by MAH due to safety reasons
4. Updates of products reference information due to safety reasons
5. Patient exposure
6. ICSR history
    - 6.1 General considerations
    - 6.2 Presentation of listed cases
    - 6.4 Tabulated summaries
    - 6.5 ICSR analysis by MAH
7. Studies
    - 7.1 Recently analysed studies by MAH
    - 7.2 New studies planned, initiated or on-going during PSUR preparation
    - 7.3Published safety studies
8. Further information
    - 8.1 Efficacy-related information
    - 8.2 Late-breaking information
    - 8.3 Risk management
    - 8.4 Risk-benefit analysis
9. General safety information
10. Conclusion

Annexes

Based on the template created I had the chance to participate in the elaboration of several PSURs for all the products approved in Mozambique. After reviewed and signed by our EU-QPPV and our vice-president, PSURs were shipped to our local contact for a further revision. After reviewed, the local contact delivered PSURs to Mozambican authorities for evaluation.

In conclusion, with the activities related to PSUR preparation and submission for Bluepharma's products approved in Mozambique, I was able to acquire

knowledge about the pharmacovigilance requirements for other countries outside EEA. Another interesting finding for me was the fact that in comparison with EEA requirements, Mozambican requirements were very similar. This may due to the fact that both entities recognize CIOMS recommendations about PSURs. Additionally, with this activity I acquired experience related to system management. Through the data-logger, whose creation I was involved, it was possible to track all PSURs to be submitted and to periodically assess the system in order to improve it.

2.2.7 Safety Variations

The reference information of a medicinal product, in an European context, is restricted to the SmPC of the medicinal product. SmPC is, as present on EC guideline on SmPC, the basis of information for healthcare professional on how to use a medicinal use in a safely and effective manner. In other words, a SmPC is a regulatory document that contains the most up-to-date scientific information regarding the medicinal product (5, 58).

The submission of a proposed SmPC upon a MAA is mandatory for all applicants. As stated on Article 10 of Directive 2001/83/EC, for generic medicines MAA the applicants are not obligate to provide the results of pre-clinical and clinical studies. Therefore, the information to be inserted on the proposed SmPC will not result from studies performed by the applicant. Instead, this information should, with exception for information protected by patent, be in accordance with information present on the available innovative's SmPC.

In accordance with Article 11 of Directive 2001/83/EC, a SmPC, for medicinal products, has the following structure (5, 58):

1. Name of the medicinal product
2. Qualitative and quantitative composition.
3. Pharmaceutical form.
4. Clinical particulars:
    - 4.1. Therapeutic indications,
    - 4.2. Posology and method of administration,
    - 4.3. Contra-indications,
    - 4.4. Special warnings and precautions for use,

4.5. Interaction,

4.6. Use during pregnancy and lactation,

4.7. Effects on ability to drive and to use machines,

4.8. Undesirable effects,

4.9. Overdose

5. Pharmacological properties:

5.1. Pharmacodynamic properties,

5.2. Pharmacokinetic properties,

5.3. Preclinical safety data.

6. Pharmaceutical particulars:

6.1. List of excipients,

6.2. Major incompatibilities,

6.3. Shelf life,

6.4. Special precautions for storage,

6.5. Nature and contents of container,

6.6. Special precautions for disposal.

7. Marketing authorisation holder.

8. Marketing authorisation number(s).

9. Date of the first authorisation or renewal of the authorisation.

10. Date of revision of the text.

As presented on the list above, a SmPC contains several types of information: from administrative information, to quality propertied, and to efficacy and safety information. By obvious reasons, information contained in Section 4 (Clinical particulars) and Section 5 (Pharmacological properties) is the most susceptible to be affect by pharmacovigilance activities.

Due to studies performed by the innovative product or by assessments of safety information performed by regulatory authorities, in particular PRAC, the information presented on those sections may need to be updated (5, 18). MAHs of generic medicines should be aware of those changes because it may be necessary the submission of variations to update the medicinal product information.

In the following sections I will describe how changes on innovatives' reference information are detected and, when necessary, how Bluepharma's products SmPC are updated using safety variations.

Authorities' recommendations

As referred, generics reference information should be consistent with those presented by innovative product. Therefore, MAHs of generics should be aware of changes in innovative product information. In Bluepharma I had the opportunity to monitor the occurrence of those changes.

When changes to references information occur, these have to be approved by Competent Authorities. EMA and HMA committees are responsible for providing recommendations for MAHs regarding new safety concerns. New safety recommendations may arise mostly by two procedures: evaluation of reference products PSURs or through signal detection. Within the weekly monitoring of changes in pharmacovigilance legislation, I had to monitor the changes in the safety information of innovative products of Bluepharma products.

Recommendations from PSUR evaluation

Depending on the approval procedure used by reference product, the institution that provides the outcomes of PSUR assessment will depend. In case of Centrally Authorised Products, PRAC and CHMP are responsible for releasing the outcomes of PSUR evaluation. In these cases a report following PSUR evaluation is performed by a rapporteur appointed by PRAC. After discussion during the monthly meeting a recommendation is published on PRAC minutes (51).

A second stage involves the approval of these recommendations by CHMP. After CHMP monthly meeting, a document with the name *Recommendation on safety variations* is published by CHMP. In this document PRAC recommendations following PSUR evaluation are discussed and approved. After their publication MAHs have thirty days to apply the recommendations (51).

In case of Nationally Authorized Products, CMDh release a document called *Summary of PSUR Assessment Report* where the outcomes of PSUR

evaluation are published. There is no legal obligation to implement the recommendations presented on Summary of PSUR Assessment Reports. However, it is suggested to implement the recommendations in ninety days after its publications (52).

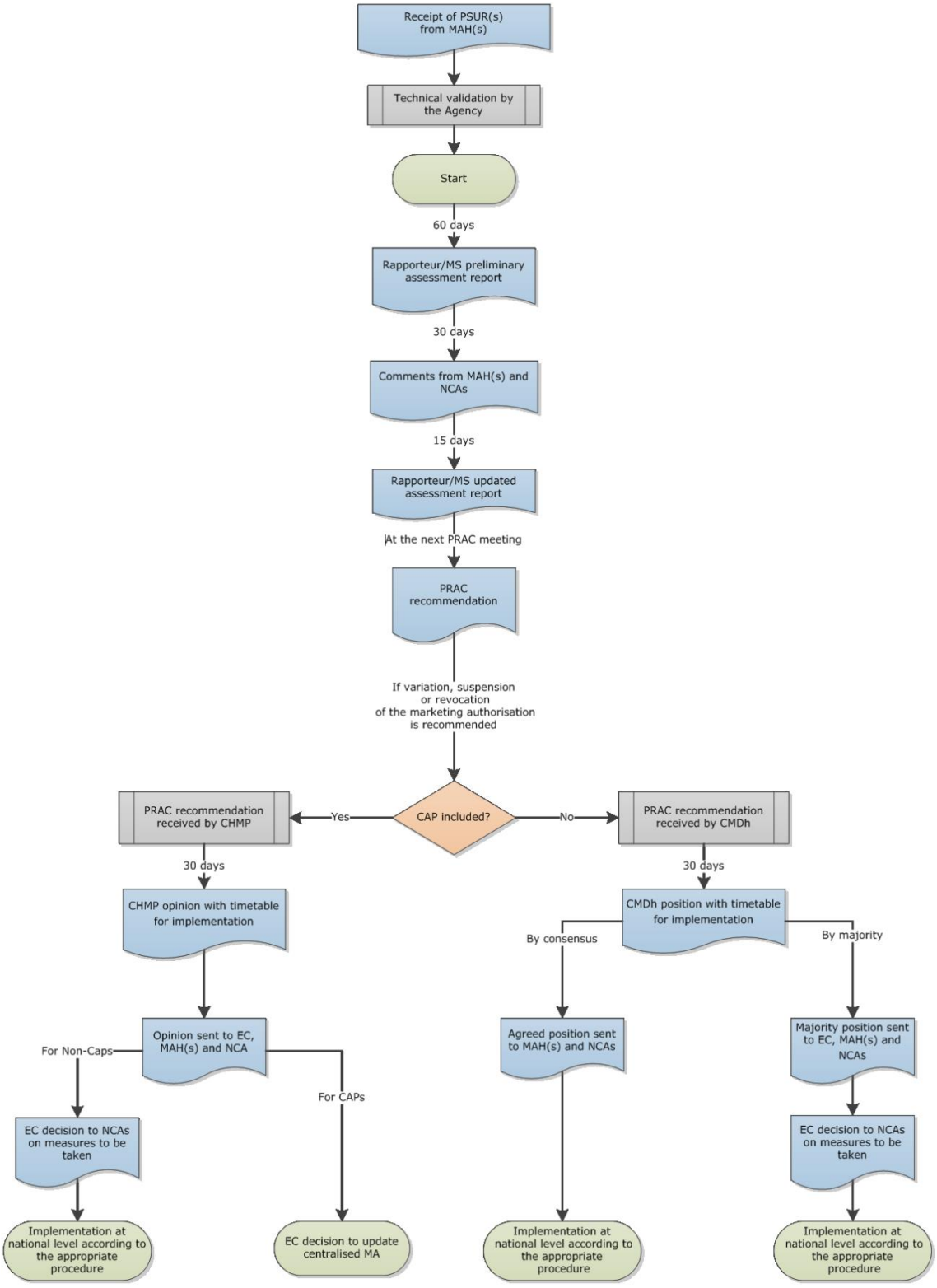

Figure 10 – PSUR assessment procedure for "EU single assessment" (51)

During pharmacovigilance legislation monitoring activities I had to take special attention to the publication of the outcomes of PSUR assessments applied to Bluepharma's products by these authorities. When I detected a publication affecting a Bluepharma's product, I had to assess how the information of the product was affected.

PRAC recommendations on Safety Signals

One of the tasks delegated to PRAC is the assessment of safety signals related to medicinal products with MA in EEA, independently the type of procedure (5, 29, 59). A signal has been described as a possible new potential causal association between an intervention and the occurrence of an event (29, 59). Each month, the Agency publishes an overview listing all signals discussed during the latest PRAC meeting and the recommendations given for each of them. This is made by the publication of a document called *PRAC recommendations on signals adopted at the PRAC meeting*. MAHs are required to proactively monitor the publication of those documents, in order to keep product's information up-to-date. The time for implementation is generally described with the recommendations (60).

For innovative products approved by national procedures, national competent authorities are expected to provide translations of PRAC recommendations on safety signals. As presented on Infarmed's *Circular Informativa No. 231/CD/8.1.6.*, Infarmed provides this service in its website. However, MAHs should use the recommendation's publication date by PRAC for submission purposes (61). If innovative product is a Centrally Authorized Product, and after further contact with Infarmed, it is recommended to implement the variations after innovative product's *European Public Assessment Report* had been updated.

One the tasks delegated to me consisted in the monitoring of the publication of PRAC recommendations. After their publication I evaluated if any changes to Bluepharma's products information occurred and if translations were already available at the time. If no translations were available I had to monitor their publication.

Other sources of safety variations

Authorities may publish safety recommendations by several other means besides the above mentioned. Recommendations following referral procedures under several articles of Directive 2001/83/EC (such as Articles 30, 31 or 107) and updating product information following the evaluation of renewal applications, are other regulatory procedures used by regulatory agencies to recommend updates to product's information.

However, those procedures did not require my monitoring. Following the outcomes of those procedures, MAHs are recommended to submit a safety variation. When a recommendation is made, MAHs are directly contact by competent authorities through an official letter. Additionally, the variation classification and time available for recommendation implementation is also provided in the notification.

Variation preparation and Submission

Requirements for the submission of variation applications are defined on Commission Regulation No. 1234/2008 (62). Requirements regarding the classification of variations are presented on European Commission Guideline on variations (43). However, since not all variations are presented on this guideline, MAHs should also be taking into account the classification of variations present on the list *CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008" when implementing safety variations* (63).

The preparation of a variation involves the following steps:

1. Identification the need for variation;
2. Internal variation codification;
3. Updating product information;
4. Preparation variation form.

In Portugal, current legislation says that variations need to be submitted through Infarmed's electronic plataform for variation submission SMUH-ALTER, as required by Commission Regulation (EC) No 1234/2008 (42, 62). This way, a variation should be submitted by creating a new variation application using

company's account in SMUH-ALTER. Following the variation application submission an e-mail alert with payment references is sent to Bluepharma. Infarmed will only start the evaluation process after the payment had been performed.

During my internship in Bluepharma I had contact with activities related to the preparation and the submission of variations. I had the opportunity to fill variation forms used during variation application. Using SMUH-ALTER platform I made entries for variation applications for Bluepharma products. Following the reception of the e-mail alert with the payment references, I learned what the internal procedure to perform payments. Therefore, I was involved in all steps needed to successfully submit a variation.

Variation application submission is a core activity in any regulatory affairs department. Within the scope of this activity I had the opportunity to prepare and submit variation applications. I understood that this is a very bureaucratic activity, since every changes proposed to product information had to be recorded in the application form. Also, I understood that special attention should be taken regarding previous approved or under evaluation variations with impact on product's information. This should be made in order to avoid the loss of information when submitting the proposed texts.

Another important learning that I acquired with this activity were the fee waivers for generic medicines. As happens in several other activities within pharmaceutical industry, MAHs of generic medicines have access to special waivers that allow them to pay reduced fees.

2.3 Regulatory Affairs activities

Regulatory Affairs represents a set of regulatory activities that are performed by MAHs in order to submit and maintain medicinal products dossiers. Although this internship was focused on pharmacovigilance-related, I had the opportunity to be in contact with some activities related to regulatory affairs field. Some of this activities involved the interaction between pharmacovigilance sector and regulatory affairs members. Other were purely related to regulatory affairs, such as exportation-related activities.

In the following section I start to describe the activities that involved coordination between pharmacovigilance sector and regulatory affairs members. On the second part of this section I will describe some exportation-related activities in which I was involved.

2.3.1 Regulatory Affairs and Pharmacovigilance

During my internship I came across with some activities that, in their nature, involved the interaction between the pharmacovigilance sector and regulatory affairs department. These were the cases of safety variations, which required coordination for their internal codification and submission, and submission of RMPs during MAA, as referred on the respective sections of this report.

Besides those activities, the coordination between regulatory affairs department and pharmacovigilance sector were also essential during the preparation and submission of renewal applications for Bluepharma's products.

In accordance with Article 27 of Decree-Law 176/2006, in Portugal a MA is valid for five years. After renewed for the first time the MA is valid indefinitely, unless otherwise specified by Infarmed. Article 28 states that renewal application should include a consolidated and updated report of product's safety profile, including an evaluation of data from reports of suspected adverse reactions, and a description of product's pharmacovigilance data (50). For that purpose, further guidance provided by Infarmed suggest MAHs to submit in sub-section 2.5 of CTD an addendum to clinical overview accompanied by a clinical expert declaration (64, 65).

Guidance regarding this addendum is provided by HMA. In according to it, it should contain at least (66):

- History of pharmacovigilance system inspections;
- Worldwide marketing approval status;
- Actions taken for safety reasons during the period covered since the initial marketing authorisation or since the last renewal;
- Significant changes to the SmPC during the period covered since the initial marketing authorisation or since the last renewal;
- Estimated exposure;
- AE data in summary tabulations;
- Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies;
- Relevant literature found in the period that might have impact benefit/risk of the medicinal product;
- Benefit/risk balance;
- Late breaking information;
- Clinical expert declaration.

During my internship I had the opportunity to be involved in the production of addendum to clinical overview to several Bluepharma's products. Since the similarity between the information that should be included on these addendums and in a PSUR it is suggested to use as guidance GVP module VII in order to fill addendum's sections. Therefore, by producing those addendums I had the opportunity to acquire more knowledge about the content of a PSUR and understand the relationship of PSURs and the addendums.

In conclusion, by coming across with these activities I got the opportunity to observe the existing relations between pharmacovigilance sector and regulatory affairs department, due to their highly regulatory nature. I additionally learned how a renewal process is conducted and the information needed to successfully complete the process.

2.3.2 MAA preparation and submission for Mozambique

The registry of medicinal products in Mozambique are regulated by Mozambican Decree No. 22/99 and by Law No. 4/98 (also referred as *Medicinal Products Law*). The medicinal products registered in this country are valid for five years and renewable in equal period (67).

Two types of MAA are allowed in Mozambique: full application or abbreviate application. An abbreviate application does not require a tighter evaluation of quality, safety and efficacy documentation by authorities as a full application, and so it presents a shorter time for approval. However, this can only be done if the product intended for registration as already an MA on a country recognized by the Mozambican republic as a reference state and is being marketed. In accordance with Mozambican legislation, Portugal is considered a state of reference. (67).

Exportation is one of Bluepharma's business activities. Mozambique is one country where Bluepharma has MAs. During my activities related to exportation for Mozambique, I learned that Bluepharma's applications for MAs in Mozambique are made using abbreviated applications.

In accordance with Mozambican guidance, a MAA in Mozambique shall include a technical dossier with the following structure (67):

- Part I – Administrative information and product characteristics;
- Part II – Chemical and pharmaceutical documentation;
- Part III – Safety documentation;
- Part IV – Efficacy documentation.

Besides the technical dossier, the application shall additionally contains the following documentation (67):

- Certificate of a Pharmaceutical Product of the medicinal product;
- Copy of MA in the reference state;
- Copy of manufacturing authorization;
- Copy of product's SmPC and mock-ups in the country of origin.

After the dossier preparation, it was reviewed by Bluepharma's submission manager for Mozambican applications. Accordingly with Article 17 of Decree No. 22/99 the application as to be delivered in person to Mozambican authority by the applicant (or its legal representative) (67). Therefore, after reviewed the dossiers were shipped product samples to Bluepharma's local representative in Mozambique. After approval by Mozambican competent authorities, local contact sent to Bluepharma a scanned copy of the MA diploma.
During my internship I had the opportunity to be involved in activities related to the preparation and submission of dossiers for MAA in Mozambique.

Within the scope of this task, I had the opportunity to be involved in one of Bluepharma's business pillars: exportation. By doing this I had the opportunity to get knowledge on Mozambican requirements for MAA and the different procedures in place that applicants can use when submitting a MAA. Since this activity involved the consultation of products' dossiers, it also allowed me to obtain a greater knowledge on CTD content (especially on Quality section).

2.4 Cosmetics and Market Surveilance

After several amendments to Council Directive No. 76/768/EEC of 27 July 1976 regarding cometic products, at November 30 of 2009 it was published in the *Official Journal of the European Union* the Regulation (EC) No. 1223/2009. This Regulation replaced the Council Directive and thereof being the legal basis for the commercialization of cosmetic products in all EEA states (68).

In order to establish an effective market surveillance system Regulation (EC) No. 1223/2009 provide to Responsible Person (i.e. a manufacturer established in EEA) and distributors clear rules about the recording and reporting of Undesirable Effects (i.e. adverse reaction attributable to the normal or reasonably foreseeable use of a cosmetic product). Those rules are presented on Article 23, which states that in the presence of serious undesirable effects (SUE), the responsible person and distributors shall without delay notify the CA. Further guidance on SUE management and reporting was provided by European Commission in 2012 on its *SUE Reporting Guidelines*. In accordance with these guidelines, SUE should be reported in no more than twenty calendar days since the Responsible Person, or the distributor, become aware of it. The report shall be accompanied by a causality assessment. In the event of SUE detected by the distributor, the guideline suggests that Responsible Person should provide assistance to distributor during causality assessment (69).

Based on this regulation and on these guidelines, I participated in the production of an internal procedure in order to manage possible SUE related to cosmetic products distributed by Bluepharma. This task allowed me to understand the safety requirements for other sectors beyond medicinal products, namely those related to cosmetics. Since an internal template for procedures was used, it also allowed to obtain a better understand on the content of this type of document and obtain experience in its production.

2.5 Scientific Service activities

In accordance with Article 156 of Decree-law No. 176/2006 (transposing Article 98 of Directive 2001/83/EC), MAHs should have in place a scientific service in charge of information about the medicinal products which placed on the market. Scientific service is responsible to ensure that Bluepharma (50):

- Communicate and provide a sample to competent authorities of all advertising activities related to Bluepharma products;
- Keep records of advertising activities performed by the company;
- Ensure that all advertising activities comply with the legal requirements;
- Ensure the adequate training of pharmaceutical representatives;
- Interaction with the authorities responsible for advertising of medicinal products in Portugal.

During my internship, I took part in activities related to advertising and promotion of Bluepharma's products to healthcare providers, within the scope of Bluepharma's Scientific Service responsibilities.

One of my major tasks related to Bluepharma's scientific service was the update of the restricted area for healthcare professionals in Bluepharma's website. When a new product is launched I had to update this area by creating an entry in website's back-office with the following information:

- Products name;
- Presentations marketed;
- Reimbursement level;
- Annexes with product's SmPC and BA/BE study results.

As present on Article 164 of Decree-law No. 176/2006, the entity responsible for an advertising activity for a medicinal product has to provide a copy of it to Infarmed in ten calendar days (50). Within this scope I had the opportunity to learn how MAHs notify Portuguese authorities when a new advertising activity is performed. I learned that MAHs shall use GPUB platform (see Figure 11) and the information needed to fulfill the notification.

Figure 11 – GPUB plartform

Besides these activities I also take part on several other scientific service-related activities, such as preparation of advertising pieces, information requests, sales representatives training and sponsoring activities (except sponsoring of clinical trials).

This was a very enrichment experience for my professional growth. With the activities related to Bluepharma's scientific service in which I was involved, I got the opportunity to complement my theoretical knowledge related to advertising of medicinal products acquired on relevant curricular units. I also learned how to use new tools related to authorities notification. Within the scope of notifications, I also understand the importance of communications between the people involved in the advertising of medicinal products. Since there are tight deadlines for notifications, it is almost mandatory to inform the scientific service immediately after an advertising piece is released into public. If the deadlines are not met Bluepharma may face monetary penalties.

3 DISCUSSION

Before my internship in Bluepharma, my knowledge about the pharmaceutical industry was very limited, particularly in the generic medicines field. And ultimately my knowledge related to Bluepharma was even scarcer.

At the begging of my internship in Bluepharma, I had obviously expectations that I was trying to accomplish and fears that I was hoping to successfully overcome. This was my first working experience and I was seeking the chance to apply the knowledge acquired in academia in real-world situations.

Internal learning sessions that new collaborators are obligate to attend were very important for me to realize how Bluepharma is structured, how processes are conducted and what Bluepharma's core activities are. In the activities that I was involved during my internship I got the opportunity to identify and understand some specificity of generic medicines that allowed the distinction from innovative medicines.

With this internship I begin my professional life related to the regulatory field within the pharmaceutical industry. Before this internship my experience was confined to curricular units attended in academia. Therefore, before this internship I had high expectations since I would have the opportunity to obtain a better and broader knowledge in this field. However, I also feared that I would not have the right profile to conduct this type of activities, since it involves a lot of interaction with other persons.

My activities, as referred throughout this report, were based on the regulatory field of pharmacovigilance, the regulatory field of pharmaceutical industry related to the safety of medicines. As referred in the previous sections there are a significant number of activities that are under pharmacovigilance scope, and although distinguishable from each other all of them are somewhat related to each other. Although not surprised by the fact, I also realized that there is not much space for innovation in the way how activities should be conducted, due to its highly regulatory basis. At the end of this internship, I realized that the activities developed in this field involve much more team work and are much more diversified than I expected at the beginning. However, there are still activities that shall be conducted in a more solitary manner. But, even in those

activities communication with other members is still needed to communicate the outcomes.

During my internship I obtained a better knowledge about the legislation regulating the pharmaceutical industry. Although during academia experience I had contact with the rules governing this industry, the way how they are applied was a novelty for me. Due to the high number of regulatory documents it is essential to choose the right ones in order to comply with the right requirements. As I had the opportunity to observe when a submission does not comply with the requirements the competent authority may invalid the submission, which may lead to the loss of part of the fee paid and always to the loss of valuable time. Therefore, when conducting this type of activities special attention should be taken when interpreting what is stated in legislation and when case contact the authorities for further explanations.

Pharmacovigilance legislation is in continuous mutation. Between 2010 and 2012 main changes occurred in EU legislation. In academia I learned what changes this reform brought to pharmaceutical industry. However, only when I started to work in the field I realized how those changes affected MAHs activities. These activities had become much more harmonized, although the burden of activities increased exponentially. Since many of these changes are still being implemented, MAHs have to be aware of their implementation. In this way I understood how important is to a MAH to be aware of authorities' publications in comparison with other regulatory activities with an older and stable legislation.

Bluepharma is a growing company, and therefore new projects are continuously being created inside the company. Many of those projects required appropriate regulatory follow-up. Either to exportation projects requiring the assistance of pharmacovigilance sector either following the acquisition of a new MA for Bluepharma's portfolio, those projects involved generally an increase in pharmacovigilance responsibilities. Since several projects were running at the same time it was easily to accumulate work. During my internship I realized that it was not possible to overrun all projects at the same time, being essential to prioritize the tasks that needed to be fulfilled. It should also be referred that this normally occurred in peaks, when new tasks accumulated with tasks normally developed by the department.

Another important learning acquired in this internship besides complying with dates is to perform tasks as pragmatic as possible. When performing a task the objective should be to comply with the requirements in the simplest way possible. This way, the task would be performed in a more efficient manner and avoid future delays, such as responses to deficiency letters from authorities.

As described in the above sections, the fact that Bluepharma's pharmacovigilance sector is located within the Regulatory Affairs department, it allowed me to obtain an experience not limited to pharmacovigilance field. I also had the opportunity to participate in several activities related to the MAA and MA management, besides the ones related to Bluepharma's and scientific service. I believe this is an advantage for my future since I get a broader experience in regulatory field related to pharmaceuticals.

Although I had felt some difficulties with new tasks allocated to me during this internship, due to their novelty to me, I surpassed them. For this mostly contributed the help provided by all department colleagues, the understanding of variables associated with the tasks and performing the same task for other products.

At the end of this internship I believe that proposed objectives were accomplished. I was able to be in contact with legislation currently governing pharmaceutical industry activities and understand how it is applied, in particular the legislation related to pharmacovigilance. I had the opportunity to obtain a deeper knowledge on regulatory affairs field, since I had the opportunity to observe and understand what activities are normally developed in this field. I was also able to give a small contribute to the success of several Bluepharma's projects. By attending and participating in several internal learning sessions I was able to understand what pharmaceutical industry is and that before a medicine is released into market several people had to participate in order to ensure its high quality standards. I also had the opportunity to participate in an internal project of learning sessions. This project was known as "Fórum da Inovação e Qualidade". Within this project, in collaboration with the other members of pharmacovigilance team, I provided several training session related to pharmacovigilance to Bluepharma's collaborators. This was a very rewarding experience for me because I had the chance to improve my presentation skills. Also, with this experience I understood the need for adapting my presentation to

the audience, since there were people with different levels of knowledge about pharmacovigilance.

As final remark, this internship allowed me to understand and gain useful experience in regulatory affairs filed, the field that I want to build my professional life in the future. Through it I gained and enhanced several technical and interpersonal skills. A list of skills acquired is provided below.

Technical skills

- EEA regulatory framework of medicinal products
- EEA regulatory framework of pharmacovigilance and scientific service activities
- Medicinal Products and Cosmetics regulatory framework
- Knowledge about the structure and content of several types of regulatory documentation (e.g. SmPC, Patient Information Leaflet…)
- Knowledge on PSUR, RMP and other pharmacovigilance-related documentation structure and content
- Knowledge on PSUR, RMP and other pharmacovigilance-related documentation preparation and submission
- Medical and scientific literature monitoring
- ICSR production and submission
- Medicinal product dossier preparation and submission
- Variation preparation and submission
- Knowledge about CTD and eCTD structure and content
- Pharmacovigilance system management
- Advertising regulatory management of medicinal products
- Preparation of specific regulatory documentation

Soft skills

- Team work
- Work under pressure
- Time management
- Sense of organization

- Pragmatism when performing a task
- Sense of responsibility
- Autonomy
- Attention to details
- Critical judgment

4 CONCLUSION

Pharmacovigilance science arose from dark moments of the pharmaceutical sector with the need to develop medicinal products with high levels of safety. Pharmacovigilance science is an every changing science that tries to adapt to the most up-to-date scientific and technological discoveries. Current tools are the result of more than fifty years of developments in the field.

Pharmacovigilance activities are mainly regulatory-based, this is they have to be made in order to comply with requirements provided by regulatory authorities. During this internship, I observed the application of the latest revolution in pharmacovigilance derived from the publication of 2010 and 2012 new pharmacovigilance legislation. This new legislation framework created new responsibilities that MAHs had to comply. Although this new legislation allowed an harmonized way how several activities are done within EEA, this new legislation had also forced MAHs to increase the allocation of resources (both human and financial) to the pharmacovigilance activities in order to comply with them.

During my internship I had the opportunity to participate in several pharmacovigilance-related activities. Most of these activities were related to each other. Therefore, coordination and communication between pharmacovigilance sector members is essential.

Due to its regulatory specificity, in Bluepharma pharmacovigilance sector is associated with Regulatory Affairs department. This allowed me to gain knowledge in several other activities related to application and maintenance of MAs.

This internship also allowed me to apply concepts discussed on academic phase. This is an advantage for me since it allowed me to obtain a better understanding of them and why they are applied.

In conclusion, this internship allowed me to get my first working experience. With it I got a better and broader understanding of several concepts already discussed in the academic setting and to understand the application of several others. Being involved in a team, this internship allowed me to develop several

interpersonal skills. Finally, this internship allowed me to develop several skills essential for my future in the regulatory field of the pharmaceutical industry.

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