Universidade de Aveiro Secção Autónoma das Ciências da Saúde
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Sara Filipa Abrantes Costa

Estágio em Estratégia e Assuntos Regulamentares de Produtos de Saúde

Training in Regulatory Strategy and Regulatory Affairs of Health Products

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Training in Regulatory Strategy and Regulatory Affairs of Health Products

Relatório de estágio apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Dra. Catarina Ramos, Responsável do Departamento de Estratégia e Assuntos Regulamentares da Eurotrials, Consultores Científicos e do Professor Doutor José Carlos Fontes das Neves Lopes, Professor Auxiliar do Departamento de Física e da Secção Autónoma das Ciências da Saúde da Universidade de Aveiro.

Dedico este relatório aos meus pais, pelos valores que me transmitiram e pelo ensinamento constante ao longo da vida, pelo incansável apoio e todo o esforço que fizeram para me ver chegar até aqui.

o júri

Presidente

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agradecimentos

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palavras-chave

Assuntos Regulamentares, Autoridade Competente, Autorização de Introdução no Mercado, Ensaio Clínico, Legislação, Medicamento

resumo

O presente relatório descreve as atividades desenvolvidas como estagiária no departamento de Estratégia e Assuntos Regulamentares da empresa Eurotrials, Consultores Científicos, empresa especializada na investigação clínica e consultoria científica na área da saúde.

O objetivo principal desta experiência de 9 meses era um primeiro contacto com mundo do trabalho, consolidando e aprofundando os conteúdos abordados no Mestrado em Biomedicina Farmacêutica.

Os Assuntos Regulamentares estão fortemente envolvidos em todo o processo de desenvolvimento do produto, desde a ideia inicial ao final do seu ciclo de vida. Tendo em conta a variedade de atividades com as quais tive oportunidade de lidar, ao longo deste relatório incluí a minha perspetiva em relação à natureza multidisciplinar que envolve a temática dos Assuntos Regulamentares.

Keywords Competent Authority, Clinical Trial, Legislation, Marketing Authorization, Medicinal Product, Regulatory Affairs

abstract

This report describes the activities performed as a trainee in the Regulatory Strategy and Regulatory Affairs department of Eurotrials, Scientific Consultants, a company specialized in clinical research and scientific consultancy in the area of health.

The main objective of this 9-month experience was the first contact with the employment world, with consolidation and deeper understanding of the contents approached in the Master in Pharmaceutical Biomedicine.

Regulatory Affairs are strongly involved in the entire process of the product development, since the initial idea to the end of its life-cycle. Taking into account the variety of activities I had the opportunity to deal with, in the course of this report I included my own perspective regarding the multidisciplinary nature of Regulatory Affairs.

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Abbreviations

ADR – Adverse Drug Reaction

CA – Competent Authority

CE – *Conformité Européene* (European Conformity)

CEIC – *Comissão de Ética para a Investigaçao Clínica* (National Ethics Committee for Clinical Research)

CNPD – *Comissão Nacional de Protecção de Dados* (Portuguese Data Protection Authority)

CPI – Critical Path Initiative

CRF – Case Report Form

CRO – Contract Research Organization

CT – Clinical Trial

CTA – Clinical Trial Application

CTAR – Clinical Trial Authorization Request

DCP – Decentralized Procedure

EU – European Union

EFPIA – European Federation of Pharmaceutical Industries and Associations

EMA – European Medicines Agency

FDA – Food and Drug Administration

JPMA – Japan Pharmaceutical Manufacturers Association

GCP – Good Clinical Practices

GMP – Good Manufacturing Practices

ICF - Informed Consent Form

ICH – International Conference on Harmonization

IMI – Innovative Medicines Initiative

IMP – Investigational Medicinal Product

INFARMED – *Autoridade Nacional do Medicamento e Produtos de Saúde I.P.* (National Authority of Medicines and Health Products, IP)

ISO – International Organization for Standardization

NME – New Molecular Entity

MA – Marketing Authorization

MHLW – Ministry of Health, Labour and Welfare

MP – Medicinal Product

MRP – Mutual Recognition Procedure

MS - Member State

NSA – Non-Substantial Amendment

PIL – Patient Information Leaflet

PhRMA – Pharmaceutical Research and Manufacturers of America

PoA – Power of Attorney

RA – Regulatory Affairs

RS & RA – Regulatory Strategy and Regulatory Affairs

R&D – Research and development

SA – Substantial Amendment

SPC – Summary of Product Characteristics

WMA – World Medical Association

WHO – World Health Organization

1. Introduction

This report is divided in 5 main chapters: chapter 1 – Introduction, chapter 2 – Regulatory Affairs Overview, chapter 3 – On-the-job training, chapter 4 – Discussion and chapter 5 – Conclusion.

In subchapter 1.1., the main objectives of this training period are detailed and a vision of the host institution is described in subchapter 1.2., including certification, organisation and services provided.

In chapter 2 an overview of Regulatory Affairs is provided focusing in some historical facts that contributed to the evolution of the regulatory environment. A contextualization is given in order to demonstrate the role of regulatory affairs and the importance of regulatory activities.

The chapter describing the on-the-job training activities – chapter 3, is subdivided according to the topics approached during these 9 months. A description of the activities performed is presented after a contextualization of each of them.

In chapter 4 – Discussion, all the topics covered in chapter 3 are explored, focusing in more subjective and critical aspects such as difficulties, lessons to retain, acquired competences, etc.

Finally, the main conclusions regarding the internship are presented in chapter 5.

1.1. Objectives and Motivation

In the scope of my Master's degree in Pharmaceutical Biomedicine, I have experienced a 9-month training period in Eurotrials, Scientific Consultants SA, more precisely in the Regulatory Strategy & Regulatory Affairs (RS & RA) department. This report is the result of that period in terms of activities performed, knowledge achieved and lessons learned.

The main objective of this training period was to bring me, as a student, closer to the reality of work, not only consolidating the knowledge achieved in both my Degree and Master, but also learning deeper through practical experience.

The training was focused in RS & RA of Medicinal Products (MP), and the objectives I established were the understanding of:

- The importance of RA in the development and approval strategy of new MP;

- The present regulatory framework of MP in Europe;
- The multidisciplinary framework of the activities developed in the scope of RA, and how this department interacts with other departments;
- What is needed to place a MP in the market, in what concerns Regulatory activities;
- The Post-Marketing Authorization RA activities.

These objectives would be achieved through the involvement in the different activities performed in the department.

1.2. Vision of the Host Institution

The internship was developed in Eurotrials, Scientific Consultants SA, a Scientific Consultant Company, founded in Lisbon in 1995 by members of academia, medical community and pharmaceutical industry. Eurotrials is specialised in clinical research and scientific consultancy in the health sector and it is currently operating in Europe, Latin America and Africa.(1)

Certification

- **2001 -** Eurotrials in Portugal obtained ISO 9001 quality certification from Lloyd\'s Register Quality Assurance with UKAS (UK Accreditation Service);
- **December 2002 -** The transition to ISO 9001:2000 was another step in the consolidation and guarantee of this work philosophy;
- **March 2009 -** Eurotrials accomplished the transition of the certification to ISO 9001:2008;
- **May 2007 -** Since then, Eurotrials has belonged to Rede PME Inovação COTEC, an initiative designed to promote public recognition of a group of SMEs whose innovative attitude and activities make them an example of creation of value for the country;
- **September 2007 -** IAPMEI recognised Eurotrials as a leading SME and so it now belongs to a group of companies considered by the organisation to be a driving force in the national economy, thanks to the quality of their performance and their risk profile.(2)

Eurotrials works with local operation centres or in partnership with other companies in Europe and Latin America, from its base in Portugal. Also, it has a wide range of partners that includes: Pharmaceutical Industry; Biotechnology Companies; Medical Devices and Diagnostics Companies; Hospitals and Clinical Research Sites; Research Institutes; Universities; CROs, Health Regulatory Authorities, and others.

Eurotrials is a company able to act in all clinical research projects and in every steps of their process, since the idea to the marketing of the product. According to this, the range of services available comprises:

Research and Development

Eurotrials operates in the development of medicines and medical devices, analyses projects (ideas and products) and draft plans for strategic and regulatory development. The purpose is to improve health research while establishing a link with the market.

Clinical Trials (CT)

Eurotrials develops and monitors clinical research projects in Europe and Latin America. The activities include: study design, protocol and Case Report Form (CRF) development (Medical Writing), implementation of CT, project management, monitoring (Phase I, II, III, and IV) and preparation of Final Study Reports.

Epidemiology & Late Phase Research

Eurotrials designs, implements and manages projects, namely Community Based Studies and Post Marketing Clinical Studies as well as cost and social impact of illness. Late Phase Studies are a major driving force behind the development of (new) medicines. They manage the associated risks and promote commercial opportunities. The main aim of Late Phase Studies resides in studying the effectiveness, safety and acceptability of medicines in the market.

Data Management

The Data Management Department has an important role in the transfer of information recorded within the CRF into clean and validated data that will be later analyzed by Biostatistics.

Biostatistics

The department provides a wide range of services adapted to the needs of each project. Statistical advice, study reports and assistance in preparing articles for biomedical journals are examples. It also ensures correct methodological development and appropriate planning in CT and guarantees the quality of protocols and reliable data processing, all of which are crucial to the success of any research project.

Regulatory Strategy & Regulatory Affairs

Regarding this department I will detail the activities performed:

Clinical Trials:

- Revision of documents (ICF/labels/IMPD);
- Translations;
- Preparation and submission of the Clinical Trial to CEIC/INFARMED and CNPD;
- Initial submission;
- Substantial/non-substantial amendments;
- Notification of End of Trial.

Marketing Authorization Application:

- Advice on Portuguese Regulatory Procedures;
- Preparation and Submission of MA Applications (National, DCP, MRP and CP);
- Liaise with Medicinal Products National Agencies;
- Provision of Official Documents Specific Procedures and Translations.

Post Marketing Activities:

- Preparation and submission of Type I and II Variations (National, DCP, MRP and CP);
- Preparation and submission of Renewals (National, DCP, MRP and CP);
- Revision of Advertisement Materials of medicinal products;
- Translations of technical documents (SPC/PIL/Labels);
- Price application to DGAE;
- Reimbursement application to INFARMED.

Other Activities:

- General Consultancy on local requirements;
- Cosmetics submission/notification of to INFARMED/CIAV;
- Medical Devices notifications to national authorities;
- Technical translations;
- Systematic reviews;
- Advisory Boards.

So, this department is responsible for the whole process of registering medicines, medical devices, cosmetics and food supplements. It monitors their life cycle and provides strategic advice and consultancy on regulatory processes. The activities/services provided will be more deeply explored in the course of this report.

Pharmacovigilance

Pharmacovigilance plays an essential role in the protection of public health, especially in assessing the risks and benefits of medicinal products. The department works in continuous cooperation with its partners, whether they are small businesses or multinational companies.

Pharmacoeconomics

Economic evaluation studies are now very important in the relationship between the pharmaceutical industry and the regulators. In addition, it is also essential to analyze return on investment in research and development, as it influences decisions on new drugs or therapeutic strategies. Eurotrials is able to answer all economic questions regarding submissions to the health authorities in accordance with methodological guidelines.

Quality

This is an independent department made up of a multidisciplinary group of auditors with vast experience in quality control and quality assurance, namely GCP audits. In addition to outsourcing, they ensure that the work of the other Eurotrials departments complies with ISO 9001:2008, the legislation in different countries, the rules of good clinical practice (ICH-GCP and GCP Directive) and any other applicable regulations.

Education and Training

This department develops training programs based upon the knowledge that has been accumulated by the several areas of the company. In close collaboration with the pharmaceutical industry, medical societies, professional bodies and clinical research departments, Eurotrials has been developing training activities that are tailored to meet the needs of different groups thus enhancing the sharing of knowledge and experience.(3)

Internationalization - Latin America

In 2001, Eurotrials expanded its services to Brazil, opening there an office to serve clients who needed clinical data from both Europe and Latin America. It was established an office in São Paulo, and Eurotrials was able to manage trials all over Latin America and also built important relationships with the Latin Regulatory Authorities.

The motivation for this expansion relied on Brazil singularity in some aspects, such as being home to one of the largest and fastest growing pharmaceutical markets in the world; having a rapidly growing market for clinical services; providing unique advantages during the CT process; its large and highly concentrated patient populations; its low per-patient cost, and its world-class healthcare facilities. All combined make Brazil an ideal place for studies in many therapeutic areas.

In 2011, after 10 years of operations in Brazil, Eurotrials started another phase of the international expansion plan with the establishment of operations in two major countries of Latin America: Argentina and Chile as a natural evolution of the Eurotrials internationalization process.(4)

2. Regulatory Affairs Overview

First I will begin by defining the science that is in the scope of this report. It is called Pharmaceutical Medicine and it can be defined as the scientific subject that deals with the discovery, research, development, evaluation, approval and commercialization of MP, biological products and other health related products.(5)

The several stages of the Drug Development (Figure 1) are equally important for the accomplishment of the mission that is the launch of the product in the market. In this report I will focus on RA and its intervention in all this process.

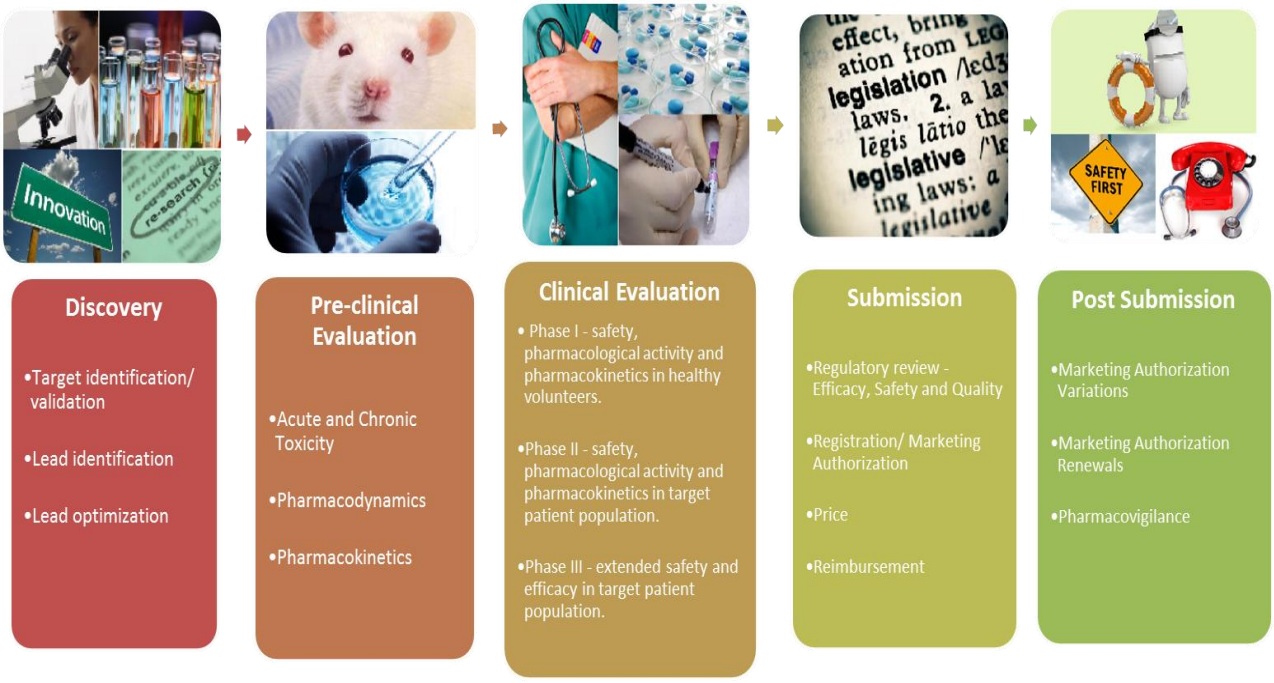

Figure 1 – Drug Development Process.

2.1. Historical Perspective

It was the sequence of historical events that contributed to reactions in terms of regulations and guidelines which nowadays, among other things, protect the integrity of subjects in CT.

A notorious example of events that compromised the human rights in the name of biomedical research was the Nazi Experiments during the Second World War.(5) Experimental starvation, induced gangrene, low barometric pressure, induced hypothermia, induced burns and wounds, are examples of atrocities that were conducted without consent of participants and caused unnecessary pain, suffering and death, beyond the absence of benefits for patients and lack of adequate scientific rationale. Those events and their unacceptable characteristics led to a regulatory and ethical response, the Nuremberg Code in 1948.(5) Above all, the Nuremberg Code was established for the purpose of preventing the atrocities of the Nazi Experiments from happening again. It argued that subject participation must be voluntary, experiments must be supported by strong scientific material, physical or mental suffering or damage is not acceptable and that the subject has the right to withdraw from the study at any time.(5)

In terms of safety we can mention many examples of events that had compromised the human rights and integrity such as Willowbrook State School in 1959 where Hepatitis virus was fed to mentally retarded children; Jewish Chronic Disease Hospital in 1963 where they injected liver cancer in terminally ill subjects; and Tuskegee Experiment between 1939 and 1970 where they witnessed to untreated syphilis in African-Americans in Alabama.(5)

The concerns in terms of safety were not only about deliberate actions but also about the amount of information that should be required before making important decisions at critical steps of development as it is: the entry in clinical development, testing special populations, etc. An example of this need is the Thalidomide event. Between 1950 and 1960 thousands of children were born with phocomelia. Thalidomide, a sedative administered for the treatment of morning sickness, produced thousands of grossly deformed newborns. It had been tested in 300 individuals with no side effects, apparently, but this was not sufficient information. As a reaction to this event it became mandatory for medicines to demonstrate evidence of efficacy before approval, evidence of safety before testing in humans, which increased the protection to humans in research and active review of test data before approval.

These are some examples and every single event had in some way contributed to the implementation of Declaration of Helsinki, which is the first possible example of a mean used to assure the safety of drug development. It has been developed since 1964 by The

World Medical Association (WMA) as a statement of ethical principles for medical research involving human subjects and it's reviewed every 4 years for any necessary changes.(5)

2.2. Regulatory Environment

The means used to assure quality of drug development have evolved over the past 30 years and nowadays we have a highly complex regulatory environment. Figure 2 shows some examples of Regulatory Bodies that exist in Europe, being Portugal here represented by INFARMED. Each country has its National Competent Authority (NCA), so, adding to the European Regulatory Bodies domain, Portugal has INFARMED as its NCA. According to World Health Organization (WHO), the general objective of a NCA is to guarantee that all MP, vaccines, blood products, biological and medical devices comply with the highest quality, safety and efficacy standards and that there is enough adequate information to promote its rational use.(5) These objectives also apply for all other regulatory bodies.

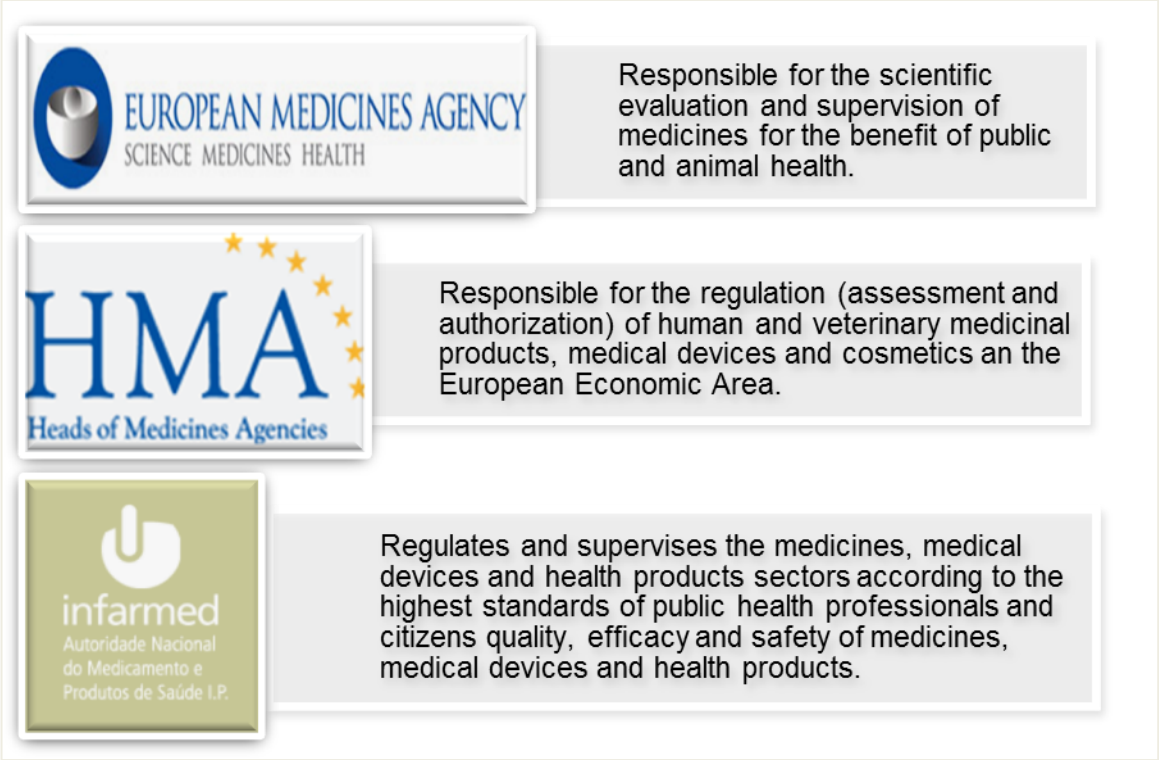

Figure 2 – Examples of Regulatory bodies.

In order to achieve gold standards, the legal aspects and guidance applicable in Europe remains in:

- **EU Regulations**

They are directly binding and directly applicable to all Member States (MS). Regulations are similar to a national law, with the difference that it is applicable in all EU countries.(6)

- **EU Directives**

Directives are of mandatory scope and they set out general rules to be transposed into national law by each country as they deem appropriate. They are part of EUDRALEX Volume 1 which compiles the body of EU legislation in the pharmaceutical sector for MP for human use.(6)

- **EU Decisions**

They are directly binding upon those addressed and they only deal with a particular issue and specifically mentioned persons or organizations.(6)

- **European Medicines Agency (EMA) guidelines**

A guideline is a community document with explicit legal basis and intended to give advice on how to fulfill a legal requirement. The objective is to provide a basis for practical harmonization. There are several types of guidelines: Regulatory, Scientific (Quality, Safety and Efficacy), Good Manufacturing Practices, Good Clinical Practices, Good Distribution Practices, etc., and they are prepared by EMA's Committee for Medicinal Products for Human Use (CHMP), in consultation with the CA of the EU MS.(6)

- **International Conference on Harmonization (ICH) guidelines**

ICH is a joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines.(7)

The ICH members are: EU, FDA, MHLW (Japan), EFPIA, JPMA (Japan) and PhRMA (biotec US), and its aim is the Global Harmonization.

The ICH mission is to make recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for

pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.(7)

2.3. The Role of Regulatory Affairs

Regulatory Affairs (RA) comprises all stages of Drug Development. Actually, I must say it is involved in the entire process:

- Early development plan;
- Approval for testing the drug in humans;
- Creating the strategic plan for the marketing of the drug;
- Handle negotiations with the Competent Authorities (CA);
- Prepare for launch;
- Monitor drugs on the market to maintain Marketing Authorization (MA).

Once a new idea is generated by a scientist for a new medicine, before this new medicine can be produced and reach patients across the world, it is necessary to make sure it is safe and effective before granting CA approval. At this stage, RA department joins the scientist so that together they can design a development plan for the new medicine.
RA knows the regulations that govern the pharmaceutical industry and they make sure there are enough tests in the plan to prove safety and efficacy of the drug according to what CA demand.
If the medicine successfully passes all trials, RA is ready to submit a new MA. At this point an enormous amount of data and documentation have been collected which will be part of the new MA. When sending data to its evaluation by CA, it is important to remember that a common goal has been shared: to market a drug that is safe and effective to use, and in fact, if the job was well done marketing approval will be granted.(8)

After MA is granted, it is time to prepare the new medicine for market launch and make sure that promotional material, packaging and delivery device all comply with the granted approvals and with the applicable legislation. The medicine is finally ready to reach patients.

However, the job at RA does not end when the medicine reaches the market. It is necessary to continue to monitor the medicines because every time a drug is optimized or

the packaging is changed, it has to be approved by the CA. Also, the CA must approve any new manufacturing facilities and RA makes sure that this process runs smoothly.
If a patient becomes pregnant, can she continue taking the medicine? RA secures the necessary additional approvals so that pregnant women, children and people with chronic diseases for example, can use the medicine.(8)

So what is the role of RA? Summing up, no matter if we are talking about early development, large scale trials, and negotiations with CA or the actual text on the packaging, RA is heavily involved from the initial product idea to the end of the medicine life.

2.4. State of the art of Pharmaceutical Medicine and Regulatory Affairs

We are currently facing a crisis in pharmaceutical industry and this is due to several crucial factors. One of the most relevant is the “productivity gap” that is the investment increasing, since we assist to very high R&D costs, and the number of new medicines decreasing. This “productivity gap” keeps up with the success rates of 11%, the lengthy of the R&D process (12/13 years) and its trend to increase (8 more years in the last decades).(9) The output stagnation also contributes to the gap on productivity, since there is a huge difficult to find really innovative new products which is a determinant factor of productivity achievement. Quoting Thomas Lonngren, the executive director of EMA: “*Those in the drug discovery business have picked all the low-hanging fruit. Now they have to reach out for the fruit at the top of the tree*”.(9)

With the increasing difficulty and unpredictability of MP development it was concluded that a collective action was needed to modernize technical and scientific tools in order to evaluate safety and efficacy. The goal is to accelerate the development of more and better medicines and there are two initiatives aiming to achieve this goal: IMI – Innovative Medicines Initiative and CPI – Critical Path Initiative.(10)
These initiatives aim to increase critical information in early phases in order to decrease uncertainty before late and more expensive phases of development (Phase II and III trials). As a result there is a reduced number of New Molecular Entities (NME) going through Phase II and III trials, but those who do have a bigger chance of succeed thus decreasing the attrition rates.(10)

The “bottlenecks” are considered as the main causes of delays in drug development and were identified as: predicting safety, predicting efficacy, bridging gaps in knowledge management and bridging gaps in education and training.(10)
These Initiatives are “living” documents being up-dated based on scientific advances and all these efforts converge in the goal to improve R&D productivity, maintain the pharmaceutical industry dynamism and to improve its conditions in terms of cost, duration and success of drug development.

This way, companies are facing an increasing need to demonstrate the value of new healthcare products. Dealing with that is becoming to rely on a multidisciplinary task that combines regulatory agencies, policy makers and payer’s requirements which are seen ever more convergent to demonstrate the advantageous benefit-risk profile of new healthcare products.(11)

In what concerns the evolution and improvement in terms of legislation, already as a result of discussions regarding the above mentioned topics, several European legal documents were under revision and approval on 2012:(12)

- Pharmacovigilance package – new Pharmacovigilance legislation (Directive 2010/ 84/ EU, Regulation 1235/2010/EU);
- Falsified medicines Directive;
- Clinical Trials Directive;
- Medical Devices;
- Veterinary medicinal products.

The EMA priorities for 2012 were:

- Continue all existing scientific responsibilities to the highest quality standards;
- Implement the new European **Pharmacovigilance legislation;**
- Prepare for entry into force of the new **falsified medicines legislation;**
- Increase **transparency** by proactively publishing more data and information;
- Strengthen **interactions** with **civil society** and engage more fully with all **stakeholders;**
- Carry out initiatives to improve the availability of medicines;
- Support the European Commission´s development of better legislation for veterinary medicines;
- Review and redesign core business processes to achieve efficacy gains;

- Foster closer cooperation with partners in the European medicines network.(12)

In this report I will try to describe the tasks performed while enhancing their critical points, as approaching also the trends in the regulatory environment as for instance changes in regulation and legislation.

3. On-the-job Training

As already mentioned, my on-the-job training was developed in the RS & RA department. This department is prepared to develop activities that occur in the whole process of registering MP for Human Use, Medical Devices, Cosmetics and Food Supplements. It monitors their life cycle by providing strategic advice and consultancy on regulatory processes.
Very close to the RA Department is the Pharmacovigilance Department. In fact, the two departments have members in common and this is a factor that facilitates the procedures because actually there is a slight barrier between them in some of their activities. This way, I also had the opportunity to develop some important activities in the scope of Pharmacovigilance.

As part of a company specialized in scientific consultancy, the activities of the RS and RA department rely on clients' regulatory needs which might be of any type from pre-Marketing Authorization to post-Marketing Authorization activities. The consultancy may be provided for MP, medical devices, cosmetics and food supplements. The requests are received, validated, if needed discussed within the department, and finally, an adequate answer is provided. Some examples of possible requests might be regulatory questions, expert reports, prices and reimbursement applications, within others. A more detailed description of the services developed in the RS and RA department will be provided further in this report while I describe the activities I performed.

As part of the Eurotrials integration programme, the first step was going through a self-training period on the company's Standard Operating Procedures (SOPs) specifically assigned for the RS and RA department.

Then, for each new topic that I had to approach, the first step was always to dedicate some time to the reading of support materials regarding those themes, in order to contextualize and prepare the task that needed to be performed.

In chapter 1.3, I provided an overview among the multidisciplinary nature of RA and fortunately I can offer in this report my own perspective about that, since I had the opportunity to deal with all this variety during the training period.

So, in this chapter, I will describe all the tasks I had the opportunity to perform. I organized them by topics and for each topic I will provide a contextualization.
Also, in Table 2 I represent an overview on the type, duration and location in time of the activities performed.

3.1. Clinical Trials Regulatory Activities

In the following sections I will describe the regulatory activities I performed in the scope of Clinical Trials.

3.1.1. Clinical Trials Application (CTA)

According to Law no. 46/2004 of August 19th, the conduction of a CT in Portugal requires a previous authorization from INFARMED and a favourable opinion from the National Ethics Committee for Clinical Research (CEIC). Also, in accordance with Law no. 67/98 of October 26th and Deliberation 333/2007 (related to personal data protection in CT with MP for human use), although the treatment of personal data (as for example, data referring to personal life and racial or ethnic origin, data referent to health and sexual life including genetic information) is forbidden, it may be allowed by means of a legal disposition or Portuguese Data Protection Authority (CNPD) - Portuguese data protection authority – authorization, when for reasons of important public interest that treatment is essential. In summary, in order to conduct a CT in Portugal, for the regulatory submission, we have to consider the submission to different important entities like INFARMED, CEIC and CNPD.
Additionally to these submissions, there is also the need for authorization from the Administration Boards of the Hospitals where the study will be conducted. The initial favourable opinion from CEIC only becomes feasible when this approval is obtained.

I started my internship in this area with an internal training session in “Regulatory Submission Process of CT”. I attended to this training session in the first day of my internship and its main objectives were to identify the entities involved in the approval of a CT in Portugal, to know what documents are mandatory to submit, to understand the timelines of approval and also the regulatory activities that occur after the initial approval.

Table 1 – Table illustrating the distribution in time of the activities performed.

	September	October	November	December	January	February	March	April	May	June
Training										
Clinical Trials Regulatory Activities										
Medical Devices										
Medicinal Products Advertising Materials										
Marketing Authorization Activities										
Prices and Reimbursement										
Pharmacovigilance										
General Regulatory Consulting										

I had then the opportunity to put in practice what I had learned by participating in the preparation of CT submissions/applications to each of the three entities involved in the process.

Clinical Trial Application to INFARMED

For a Clinical Trial Authorization Request (CTAR), it is necessary to submit a cover letter addressed to INFARMED, written in Portuguese, duly signed, containing in the header the EudraCT number, the CT protocol number designated by the sponsor and the corresponding study title.
The EudraCT number is a study specific identification number, which must be obtained from the CT European database (EudraCT) before submitting the CTAR to INFARMED.
So that a CTAR is considered to be valid, it must comply with the applicable legislation and must contain all the elements required by INFARMED:

- Essential Information
  - EudraCT number confirmatory document;
  - Cover letter (in Portuguese);
  - Application Form;
  - XML File referring to EudraCT database (full data set is required by INFARMED);
  - Protocol updated version;
  - Investigator Brochure;
  - Investigational Medicinal Product (IMP) Dossier;
  - Summary of Product Characteristics (SPC) (for products with MA);
  - List of MS Competent Authorities where the application was submitted and corresponding decision (if applicable);
  - Copy of CEIC's opinion (when available, but usually not available because the process occurs in parallel with CEIC)

- Additional information for special situations
  - Authorization letter that allows the CT applicant to represent the sponsor. This document is applicable when Eurotrials submits a CT on behalf of the study sponsor. It is designated "power of attorney" (PoA).

- Specific Information for the application in Portugal
  - Regarding the CT participants
    - Informed Consent Form (in Portuguese language);
    - Participant Information Leaflet (PIL) (in Portuguese language).
  - Regarding the study protocol
    - General description of all active studies with the same IMP;
    - Study evaluation by external experts (when available).
  - Regarding the IMP
    - When the IMP is manufactured in the EU and does not have MA in the EU:
      - Copy of the manufacturer authorization.
    - When the IMP is not manufactured in the EU and does not have MA in the EU:
      - Declaration from the qualified person, stating that the manufacturing place is in conformity with the EU GMPs;
      - Copy of the importer authorization.
    - Certificate of Analysis of IMP;
    - Viral safety studies;
    - Label samples in national language;
    - Special authorizations (when applicable);
    - TSE Certificate;
    - GMP conformity certificate of the biological active substance (when applicable).
  - Regarding the site facilities and staff
    - Curriculum Vitae of Investigator-Coordinator;
    - Curriculum Vitae of all Principal Investigators;
    - Information about the collaborators.
  - Regarding financial issues
    - Predicted dispositions for repair and compensation for damages or death imputed to CT;
    - Insurances or compensations that cover the investigator and sponsor responsibility;
    - Compensation to investigators and participants;
    - Contracts between sponsor and study sites.

Clinical Trial Submission to CEIC

The submission to INFARMED and CEIC is usually done in parallel. The process is similar although they have some distinct aspects to consider. I will approach this differentiation further on section 3 “Discussion” of this report.
The submission to INFARMED and CEIC is made in paper and in CD-ROM, as following:

- In paper
  - The cover letter of CTAR;
  - EudraCT number confirming document;
  - Proof of Fee payment;
  - CTAR form duly signed;
  - Verification List.

- In CD-ROM
  - Protocol and Amendments;
  - Investigator Brochure;
  - XML File;
  - IMP information;
  - Other elements contained in the Verification list.

The documents submitted in the CD-ROM are presented in a pre-defined and organised structure of folders.

For both submissions above mentioned, the tasks I developed were to verify that all documentation needed were ready to submit and according to the legislation, to place all documents in the corresponding folders following the predefined structure and organization and to write the cover letter and list of documentation submitted, accordingly. Also, the cover letter was translated into English in order to be sent to the client before the submission, so that he could give permission to carry on with the process.

Request for authorization to CNPD

The authorization request from CNPD is a simple procedure since the application is submitted electronically, filling in an online form, available on the CNPD website. The information requested is about the responsible entities for treating the collected data, the purpose of the data collection, type of data collected, information about whether the data is transferred to other countries or not, how data protection is guaranteed, among others. The payment to CNPD must be ensured within 3 days from the submission.

Other developed activities in the scope of Clinical Trial Authorization

To comply with the national legislation, there are some local adaptations that we must perform in the master documentation that ET receives from the client. One good example of that is the local adaptation that must be made to the Informed Consent Form (ICF). I carried out a revision of an ICF to verify that it was according to the national requirements which are:

- Include the EudraCT number, protocol code and sponsor identification;
- Include the contacts of the Investigator;
- Limited use of abbreviations;
- Express the volume of blood in “ml”, not in “teaspoons” which is usually used in English versions;
- Use the expression “lançar a moeda ao ar” (meaning “flip the coin”) to express treatment randomization;
- Include a field of signature for a second witness.

Additionally, the ICF should refer to Law no. 46/2004 of August 19th through expressions that draw attention specifically to the data protection, CEIC contacts, policy insurance, the fact that no payment will occur except for reimbursement of related expenses.
I also performed a revision of an ICF translation (English to Portuguese), paying attention to the compliance of the content, in addition to the requirements of Portuguese legislation that I mentioned above.

3.1.2. Regulatory Activities after Clinical Trial Authorization

In this section I will present the regulatory activities that are needed after CT authorization.

Notification of first patient enrolment

As already mentioned, the initial favourable opinion from CEIC only becomes feasible when approvals from each Hospital Administration Boards involved in the study are obtained. In addition to this, and according to Law no. 46/2004 of August 19th, the beginning of the CT in the corresponding site must be notified to CEIC. According to it the beginning of a CT corresponds to the date of enrolment of the first patient in that site.
This way, I had the opportunity to collaborate in the writing of the notification letter communicating to CEIC the date of enrolment of the first patient in one specific site. This letter was also translated to English to be sent to the client so that he would be informed about the process.

Notification of Amendments to the Clinical Trial

The amendments to CTs can be substantial (SA) or non-substantial (NSA) (Table 2). Amendments to the trial are regarded as "substantial" where they are likely to have significant impact on the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial. In all cases, an amendment is only to be regarded as "substantial" when one or both of the above criteria are met.(13) In what concerns NSA it is not mandatory to notify them, but they must be registered and available if requested in case of inspection. According to the Eurotrials procedures (SOPs) all NSA must be notified by default. Nevertheless, in the end, it is the sponsor's responsibility to decide if they want the NSA to be notified or not. To avoid a high volume of notifications, it may be considered the inclusion of NSAs in future SAs applications.

Table 2 - Examples of Substantial and Non substantial amendments

Amendments as regards the Clinical Trial protocol(13)	
Substantial	**Non substantial**
Change of main objective of the CT.	Changes to the identification of the trial (change of title, etc.).
Change of primary or secondary endpoint which is likely to have a significant impact on the safety or scientific value of the CT.	The addition/deletion of exploratory/tertiary endpoints.
Addition of a trial arm or placebo group.	A minor increase in the duration of the trial (<10% of the overall time of the trial).
Change of IMPs, IMPs dosing or IMPs mode of administration.	Minor clarifications to the protocol.
Change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment.	Correction of typographical errors.

In my internship I had the opportunity to perform a NSA notification, which consisted in the participants and investigators insurance policy renewal for a specific study.

In what concerns SA, they can only be implemented after CEIC's favourable opinion, CNPD's approval and/or INFARMED's approval (whenever applicable).
For the submission of a SA the procedure should be first to evaluate whether new documents are necessary or actual documents need to be changed. Then, if changes are implemented on any documents, we should always create versions with changes

highlighted, paying attention to correctly mention the version and date in the name of the documents.
The documents to submit with the request are:

- In paper
  - The cover letter;
  - Proof of Fee payment;
  - Amendment Notification Form;

- In CD-ROM
  - Changed informative elements;
  - Support information to the changes;
  - XML File (if applicable).

I participated in the preparation of a SA related to CT arrangements, where a new study site was added. Regarding this I performed the translation to English of the notification letter in order to keep the client informed about the process. For this amendment the following documents were involved:

. Curriculum Vitae of the Principal Investigator;
. Protocol signature pages;
. Declaration regarding the conditions of the new study site;
. Financial contract with the new site;
. Updated insurance policy.

None SA with impact in the protocol came up, so I studied one as an example to see what documents or changes were necessary to submit. In this case the protocol amendment implied an update to the ICF. The cover letter stated the changes made and the facts that they result from. Most importantly, the ICF should be submitted in a version with changes highlighted and in the final version.

Development Safety Update Report (DSUR)

According to Law no. 46/2004 of August 19th, during the CT and until its conclusion, the sponsor must annually present to INFARMED and CEIC a list of all suspected serious adverse reactions during that period, and also a report regarding participants' safety.

According to “ICH E2F – Note for guidance on development safety update reports”, the DSUR is intended to be a common standard for periodic reporting in drugs under development among the ICH regions. During the clinical development of an investigational drug, periodic analysis of safety information is crucial to the on-going assessment of risk to trial subjects. This shows the importance of keeping regulators informed about the results of such analyses and the evolving safety profile of an investigational drug. This way, the main objective of a DSUR is to present an annual review and evaluation of pertinent safety information collected during the reporting period.
Given the importance of this issue, although none submission happened during my training period, I took an example of a notification to learn how this process usually happens.

Declaration of the end of Clinical Trial

According to Law no. 46/2004 of August 19th, the end of the CT must be notified to INFARMED and CEIC within 90 days. The end of CT is defined in the protocol and the sponsor has to make an end of trial declaration when the complete trial has ended in all MS / third countries concerned. The sponsor must also within 1 year after the conclusion of the CT, submit to INFARMED and CEIC a summary of the CT Report.(13) Regarding this step, I did not have the opportunity to perform any notification of end of CT.

Label related activities

Regarding the label of the IMPs, the Law no. 46/2004 of August 19th, states that all information that appears in the outer packaging of IMPs or, where there is no outer packaging, on the immediate packaging, must be written in Portuguese. The information may also appear in other languages too.
In this context, the task I performed was to translate the label information to Portuguese in order to comply with the legislation. For the content of IMPs labels it must be taken into consideration Annex 13 “Investigational Medicinal Products” of the GMPs, the standard terms (for pharmaceutical forms, route of administration and containers) and the Quality Review of documents (QRD).

Management and archive of information

Given the complexity of the whole process of a CT execution, with so much documentation being exchanged between sponsor, consultants and all entities involved, it is very important to maintain all documentation on tracking, organised, duly identified and most important, compliant with all legal requirements. Whenever a document is sent or arrives, it is crucial not to lose the tracking of it, naming it properly and archiving it adequately. Every time the sponsor asks us for information or any documentation it is easier to find and send them the correct information. I was involved in a specific supply of study documents to the sponsor, where I had to check the tracking file and the dossier in paper and electronically, to confirm that it was everything in order to be sent to the sponsor. After that I contacted with the sponsor by email, to send him the documentation he asked for.

After having experienced all these activities related with CTs, I performed a multiple choice evaluation test on “Regulatory Submission Process” to close this stage of my internship.

3.2. Marketing Authorization Activities

The objective of several years of MP development is to place the product on the market. This way, to market medicines in the European Economic Area (EEA) a Marketing Authorization (MA) is needed. In the next sections I will present the MA related activities.

3.2.1. Marketing Authorization Application

A MA can either be granted by a Member State (MS), a country from the EEA or by European Medicines Agency (EMA) and the Marketing Authorization Holder (MAH) must always be established in the EEA. So in the EEA, the same legal, scientific and operational requirements, grant same conditions for accessing the marketing. The main objectives of this European system are:

- To obtain a unique market for MP;

- To protect and promote public health ensuring the safety, efficacy and quality of MP;
- To improve access to better and new MP;
- To provide the same information about MP for patients and healthcare professionals;
- To assure harmonization of use of MP across EU;
- To minimize divergences in assessment of MP;
- To assure harmonization of the legal, scientific and procedural criteria for MA.(6)

The assessment of the Marketing Authorization Application (MAA) by a competent authority regards quality, safety and efficacy data. If the medicine has a positive benefit/risk balance and if it is of quality has efficacy and is safe, then, it has the conditions to be approved.
When the MA is approved, it is issued a MA certificate with details about the MP (e.g. qualitative and quantitative composition, manufacturers and dimensions of pack size), and a Summary of Product Characteristics (SPC), a Package Information Leaflet (PIL) and the Labeling are approved.

In Europe there are 4 different procedures that can be used to obtain the MA of a MP:

Centralised Procedure (CP)
The MAA is evaluated and managed by EMA and the MA is valid in all MS of the EU.

Mutual Recognition Procedure (MRP)
This procedure is based on national decisions already existent. The first step in this procedure is the grant of a MA in one MS of the EU (Reference Member State), which performs the first evaluation and approves the MP nationally. This approval is the support for the application to be submitted in other MS - Concerned Member States (CMS).

Decentralised Procedure (DCP)
This procedure can be used only when the MP does not have MA in any MS. Although the application is submitted in several MS at the same time, one of them will be appointed as the Reference Member State and will be responsible for the elaboration of an evaluation

report. The other MS involved (the CMS) will comment on this report, which will be updated, when considered necessary.

National Procedure

When it is intended to approve the MP in only one MS, it should be used a purely national procedure. The MA will be evaluated by the CA of the country where the MAH wants to obtain a MA approval.(6)

In the scope of Marketing Authorization, the activities I performed were as follows:

Patient Information Leaflet and Labels artwork revision

After MA assessment, there is a phase of discussion with INFARMED regarding the product information (SPC, PIL and labels), and in the end of the MA we will have an adequate approved Portuguese version of all the texts.

After that, it is time to start the production of PILs and labels artworks to place the MP on the market. The role of the regulatory affairs professional at this point is to review the artworks and confirm that they are in accordance with the approved information, and this was one of the activities that I performed during the training period. After that revision, the PIL and labels can be produced with certain that they are according to the approved texts by INFARMED.

Marketing Authorization Certificate revision

As I have already mentioned, when the MA is approved an Authorization Certificate is issued with details about the MP (e.g. qualitative and quantitative composition, manufacturers and dimensions of pack size).

I performed the revision of the MA certificate (together with the approved SPC, PIL and labels), as an important final step, in order to verify the compliance of the information contained in the certificate and actually approved, with the information submitted to INFARMED and intended to be approved. It might happen that some inconsistencies are found. After INFARMED sends the MA notification, the MAH has a limit of 10 working days to correct any typos or other wrong information found in the certificate.

3.2.2. Variations to Marketing Authorizations

During the MP life cycle, the MAH is responsible for monitoring and updating the dossier of the MP having in consideration the technical and scientific progress. This update includes any variations to the dossier which are necessary so that the MP can be manufactured and controlled through scientific methods globally accepted.
Such amendments may involve administrative or more substantial changes, and procedures for the preparation and approval of such amendments are ruled by specific EU Regulations and National legislations. We can categorize variations in type IA, IB and II and these variations must be notified / approved by the CA. For MPs that have been authorised nationally but not via MRP or DCP, procedures are ruled by national legislation. Such procedures may not be exactly the same as those set out in Community legislation.(14)

It might happen that a variation (type I or II) requires consequential change to the SPC, labelling or PIL, and this will be considered as part of the variation and the corresponding updated documents should be provided in the variation application.

In this chapter I will focus the cases that I had the opportunity to deal with.

Variations on Marketing Authorization obtained by National Procedure - Portugal
Minor variations – type IA and IB

The classification of variations as type IA and IB is defined in the local legislation (Law-Decree 176/2006).
These variations, in the scope of national procedures, are submitted online through a system of submission of variations available in the website of INFARMED, I.P.
Regarding Type IA national variations, I was responsible for submitting a group of several variations which purpose was the change in the name of the MAH. The variation was submitted for the total portfolio of the MAH and given the volume of work required it had to be performed in different circumstances. Instead of working in Eurotrials' facilities I had to work in the client's facilities during 1 month in order to perform this activity. The tasks performed in this scope were the preparation of the cover letter for the submission, the fee payment, the filling of the online form and also the update of the product information (SPC, labelling and PIL) with the new MAH name, for all products. The submission was

performed online in INFARMED's website thought the electronic system of type I national variations submission.

Variations on Marketing Authorization obtained by Decentralized / Mutual Recognition Procedure

Major variation - type II

In this scope, I was involved in the preparation of the submission of a type II safety variation requested by the Authorities.

Type II safety variations requested by CA are a safety measure which foresees the update of the Product Information (SPC, labelling and PIL) of the MP, for which a potential safety problem have been identified. This way, INFARMED notifies the MAH of the MP through an official letter, so that they submit the corresponding variation application. They also inform about the text containing the new safety information to be included in the product information.

So, to perform this activity it was necessary to prepare the texts (SPC, PIL and label) according to the above mentioned topics.

In some cases, the tasks requested by the client in the scope of the submission of a variation, only comprised the preparation of the submission according to the national requirements, which means, not involving modification of any documents to be submitted. In this case, the whole package is supplied by the client / MAH, and we only have to perform the submission of the application. The tasks developed in this scope were:

- The fee payment, that must be performed in advance;
- The elaboration of the cover letter for the application;
- The filling of the application form;
- The submission in electronic format (2CD's) of all documentation to support the variation.

3.2.3. Marketing Authorization Holder Transfers

Another MA related activity is the Marketing Authorization Holder transfer which consists in changing the MAH of a MP. In this case there is a change of the legal entity and it is not only a change in the MAH name.

Regarding this activity, I was involved in the preparation of a MAH transfer for a MP. The first step was the fee payment for this procedure that must be performed in advance to the submission. After that I prepared the submission performing the verification of the supporting documents sent by the MAH comparing them with INFARMED's requirements. It involved communication with the client requesting additional documents that were missing to perform the application accordingly.

3.2.4. Marketing Authorization Renewal Applications

In Europe, a MA is valid for 5 years, and it is renewable upon submission of a renewal application by the MAH. This renewal application must be submitted 180 days before the authorization expires. For the renewal, the MAH should present a consolidated and updated dossier of the process with all information gathered during the life-cycle of the MP regarding quality, efficacy and safety, including all variations submitted since initial MA.

Once renewed, the MA is valid for an unlimited period of time unless the CA decides based on Pharmacovigilance data of the MP, that another renewal procedure is necessary.

I was involved in the preparation of a renewal submission for a MP and the tasks I performed were mostly regarding the documentation to submit. The client requested information about the documentation needed for submission, according to Portuguese requirements. We provided the client that information and we also gave support in the preparation of some local documents.

3.3. Medicinal Products Price and Reimbursement Applications

The activity developed in this scope was regarding a group of generic MP intended to be introduced in the market and I was involved in the strategy planning for price and reimbursement applications. The purpose was the elaboration of a report compiling data

referent to Portuguese requirements in these procedures, with a proposal of strategy for the corresponding company to follow.
For developing this activity, I started by collecting from national legislation some assumptions for price and reimbursement applications of generic MP in Portugal.

According to the Portuguese pricing legislation currently in force, the price of a generic medicinal product must be at least 50% lower than that of the reference product. In cases where the ex-factory price of all the pack sizes of the reference product is lower than 10€, the price of the generic MP must be at least 25% lower than that of the reference product. This applies to all generic MP until the creation of the homogenous group. When the first generic of a reference medicinal product is effectively put in the market (i.e. the product is in the market, not just authorised), a homogenous group is created and the prices of the medicines included in the homogenous group are regulated by a reference pricing system. The reference price corresponds to the mean price of the 5 lowest priced medicinal products (generic or not) in that group. After creation of a homogenous group, the price of generic MP included in that group must be equal or lower than the reference price.
The reimbursement of MP in Portugal depends on the therapeutic superiority or equivalence and on the economic advantage of the MP as compared to others MP used as “comparators”.
If a given MP has the same qualitative composition in active substance of other reimbursed non-generic MP (comparators), its reimbursement is dependent on a 5% price reduction as compared to the lowest priced non-generic MP used as comparator. In the cases where there is already a homogenous group, the price of new MP must be at least 5% lower than the lowest priced generic MP included in that homogenous group which has least 5% of market share. From the 5th generic MP for a given reference MP, inclusively, the price of the generic MP must be lower than the maximum price of the generic MP which reimbursement application was submitted immediately before, regardless of the authority’s decision on that procedure.
The Portuguese legislation defines which pack-sizes may be reimbursed, based on 1) duration of therapy, 2) monitoring requirements and 3) pharmaceutical form.
In the specific case of generic MP, to be reimbursed, the pack size and strengths must be in line with the pack sizes of similar MP (same active substance/same pharmaceutical form) already reimbursed in Portugal.

The reimbursement of additional pack-sizes and strengths is dependent on the justification of therapeutic added value, taking into consideration the approved indications and posology.

Once collected these assumptions, they were included in the report sent to the client to inform them about the legal frame in Portugal. Besides that, this rational represented the basis for the strategy to be followed.

Regarding prices, the first thing to check for is if the price calculation will be based on the price of the reference medicinal product or if it will be based on the reference price of the existing homogenous groups. Based on that, we defined for which strengths and pack-sizes prices we would apply for.

In what concerns reimbursement, attention should be paid regarding the strengths and pack-sizes to apply for, because the MAH's have 6 months to place the products on the market after the reimbursement approval, otherwise they will lose the reimbursement for all strengths and pack-sizes. So, before applying for reimbursement, it is necessary to discuss with the client what he really wants to have reimbursed and is able to place on the market.

So, in the report we presented the client with a list of the strengths and pack-sizes for price and for reimbursement applications, as a result of a case-by-case analysis based on the assumptions mentioned before. This was the proposal made to the client, and then we waited for their feed-back in order to obtain a green light to move forward with the strategy and apply for prices and reimbursements according to their final decision.

3.4. Prior Assessment Application

Regarding MP for human use in hospitals, a different approach is applicable. According to the current legislation in Portugal, the acquisition and use of new medicines subject to restricted medical prescription by the hospitals of the National Health System is ruled by Decree-Law 195/2006 of 3rd October, republished on 13th May 2010.

With the purpose of rationalize resources in the hospitals, it is consider necessary to subject these MP to a "Prior Assessment" (equal to that used for the other reimbursement MP), before their acquisition by hospitals. This assessment is performed by INFARMED.

The decision on the Prior Assessment application depends on the demonstration of:

- Therapeutic added value – **Pharmacotherapeutic report**;
- Economic advantage – **Pharmaco-economic report**.

The above mentioned reports should contain:

- The therapeutic added value associated with the MP having as a reference other approved therapeutic alternatives;
- The maximum price considered adequate to the MP;
- The economic advantage of the MP when comparing with the available therapeutic alternatives, documented with the available scientific evidence or economic evaluation study;
- The budget impact;
- Other relevant elements.

The decision about prior assessment applications belongs to INFARMED. A refusal means that the MP cannot be acquired by the public hospitals of the National Health System. The approval implies the formalization of a contract between INFARMED and the MAH, meaning that the hospitals can acquire the corresponding MP however this is not binding for the hospitals to acquire the MP.

Regarding this matter, the activity I performed was the preparation of a document to be sent to the client providing information about the documentation required for a Prior Assessment application. The result was the following list of documents:

- MA certificate and document mentioning the national codes;
- Approved SPC and PIL;
- Approved label;
- Approval for variations to the MA certificate, SPC, PIL and label;
- Power of Attorney providing authorization to Eurotrials to submit this application on behalf of the client;
- Therapeutic indications for which the prior evaluation is requested;
- Document with information about the MP in other EU Member States, regarding:
    - Prices currently approved and corresponding regimens;
    - Reimbursement, including possible special regimens;
- Price structure taking into consideration the investigation, production and promotion of the MP (i.e. how was the price established?);

- Maximum proposed price for marketing purposes;
- Pharmacotherapeutic report (clinical added value report);
- Economic evaluation;
- Other important elements for the assessment:
    - Average cost of treatment with the MP;
    - Expected number of patients to be treated in the first and second years of marketing (having in consideration the impact of the disease in Portugal and in the hospitals and the percentage of market share taking into account the available alternatives);
    - Other.

Regarding the Pharmacotherapeutic and Pharmaco-economic reports, I only had the opportunity to read and analyzing some examples of previous cases submitted to INFARMED.

3.5. Medicinal Products Advertising Materials

The group of laws and codes of practice that govern the advertising of medicinal products in Portugal are as follows:

- Decree-Law 176/2006, 30th August 2006 ("Medicines Code"), which transposed Directive 2001/83/EC, of 6th November 2001, on the Community Code relating to medicinal products for human use.
- Decree-Law 330/90, 23rd October 1990, as amended ("Advertising Code"), which sets-forth the Portuguese advertising rules in general, is subsidiary applicable to the advertising of medicinal products in all matters not specifically provided for in the Medicines Code.
- Resolution 044/CD/2008, 7th February 2008, issued by INFARMED and which came into force on the 1st April 2008, approved the "Advertising Regulation".
- At a deontological level, the Apifarma Code of Practice for the Pharmaceutical Industry ("Apifarma Code"), approved by the Association of the Portuguese Pharmaceutical Industry (Apifarma), must also be considered.

The advertising of MP is defined in the Medicines Code as any form of information, surveying or inducement with the purpose or effect of promoting the prescription, supply, sale, purchase or consumption of such products.

In particular, it shall include:

- Advertising of MP to the general public and to persons qualified to prescribe or supply them;
- Visits by medical sales representatives to persons qualified to prescribe MP;
- Supply of MP samples;
- The provision of inducements to prescribe or supply MP by offering gifts or promises of any benefit or bonus, whether in money or in kind (except when their intrinsic value is minimal);
- Sponsorship of promotional meetings attended by persons qualified to prescribe or supply MP;
- Sponsorship of scientific congresses attended by persons qualified to prescribe or supply MP and in particular payment of their travelling and accommodation expenses in connection therewith.

Nevertheless, the following situations are not considered as advertising of MP:

- The labeling and the accompanying package leaflets;
- The correspondence used to answer a specific question about a particular medicinal product, possibly accompanied by material of a non-promotional nature;
- Factual or informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, since they include no other information about the product;
- Information relating to human health or diseases, as long as there is no reference, even indirect, to medicinal products.

Also important to refer is the fact of being forbidden the advertising to the general public of MP subject to medical prescription or containing substances defined as psychotropic or narcotic by international convention.

In this field, the responsibility of the RA department is to ensure compliance of advertising materials with the legal requirements contained in the legislation. The main points to consider are that all parts of the advertising of a MP must comply with the particulars approved in the SPC and also that it shall encourage the rational use of the MP, by

presenting it objectively and without exaggerating its properties. Also, the advertising information shall not be misleading.

I was involved in the revision of MP advertising materials to persons qualified to prescribe or supply them. Additionally to the above mentioned points to consider, according to Decree-Law 176/2006, this kind of advertising material should include:

- The name of the MP;
- Essential information compatible with the SPC;
- The supply classification of the MP;
- The reimbursement regime.

The essential information compatible with the SPC means the group of SPC elements considered mandatory to be included in the advertising material. This information may be written differently but cannot be divergent from those established in the approved SPC. Those elements are:

- Name of MP;
- Qualitative and quantitative composition;
- Pharmaceutical form;
- Therapeutic indications;
- Posology and method of administration;
- Contraindications;
- Undesirable effects;

If relevant from a clinical point of view, it will also be important to include information about:

- Special warnings and precautions for use;
- Interactions with other medicinal products and other forms of interaction.

For the revision of those materials a check list, prepared by the RA department, which include all these criteria, was used in order to help in the performance of this task.

The MAH should notify to INFARMED the advertising materials in circulation and this is made by using a specific electronic tool available in the INFARMED's web site.

The advertising materials notification to INFARMED is another activity performed by Eurotrials RA department

I had the opportunity to perform the notification of several materials. This is a procedure that has to be done within 10 days from the date of the first publication of the material.

The information to provide includes:

- Name of MP;
- The legal representative (when different from the MAH);
- The entity responsible for the advertising;
- Name of the material;
- Internal code (for material identification);
- Material description;
- Means of diffusion;
- Type of material;
- Local of diffusion;
- Target audience;
- Beginning of distribution;
- End of distribution;
- Support documents (optional)

3.6. Medical Devices

The regulatory system for medical devices (MD) is quite different from that for pharmaceuticals. In order to place a MD in the EU market it is necessary that the MD has been granted a European Conformity (CE) mark. This does not involve the assessment of the product by a medicines agency or the grant of a marketing authorization. Instead, the onus of ensuring and declaring that a product conforms to the legal essential requirements belongs to the manufacturer, or to an independent technical organization, known as a Notified Body, depending on the classification of the MD.(5)

The essential requirements relate to the safety in use of the device, including labeling requirements, but are principally expressed in terms of scientific and technical performance characteristics. Conformity of a device with the essential requirements is demonstrated by affixing a CE mark in the device. The CE mark assures that the product complies with all legal requirements and acts in effect as the passport that authorizes the device to be placed on the market and to circulate freely within the European Economic Area (EEA).(5)

According to the legislation, it is only possible to place in the market devices that, cumulatively:

- Satisfy the essential requirements established on appendix 1 of the corresponding Decree Law;
- Exhibit CE mark;
- Have been subject to the conformity assessment.

Notification/registration of Medical Devices

From the CA perspective, in the scope of market supervision it is essential to be aware of the existing devices and corresponding responsible for placing it in the market. This way, the Portuguese legislation established the obligation for notification/registration of MD that are launched and being marketed in Portugal.

This way, the RA department offers support in the notification/registration of MD marketed in Portugal in the INFARMED's website. This on-line procedure was recently implemented as an answer to the legal requirements established in the European Directives and applicable National Legislation.

Both manufacturer and distributor must notify/register the MDs that are being marketed in Portugal. The registration for manufacturer differs from that for distributers. For example, the manufacturer registration is performed in paper for Class I MD and on-line for the remaining classes, for wholesalers the registration is in general performed on-line.

The first step in my training regarding this subject was an internal training session in "Medical Devices registration in Portugal" which gave me an introduction to the procedure. Being familiarized with the matter, I performed the quality control of the registration, previously performed by data entry staff. The quality control consisted in verifying if the registration of the MDs was well performed taking into consideration the legal requirements.

Revision of Labels and Instructions for use

Another activity performed in the scope of MDs was the support in the revision of the labels and instructions for use for some products. I performed the translation or the

translation review of the information as per request of the client. Also a revision in terms of content was performed in order to verify the conformity according to the legal national requirements described in Decree Law Nº 145/2009 of 17th June.

3.7. Pharmacovigilance

Given the close collaboration between RA and Pharmacovigilance departments I also had the opportunity to be involved in some activities concerning Pharmacovigilance during my training period.

According to World Health Organization (WHO), Pharmacovigilance comprises the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems.
I have already made reference to the Thalidomide disaster in the Introduction of this report namely in the historical perspective of Regulatory Affairs, and that can be used as an example to illustrate the need for Pharmacovigilance activities. Actually, it was in the awake of the Thalidomide disaster that WHO was requested to take an active role in assuring the safety of drugs and so, Pharmacovigilance was officially created.

The main thing to have in consideration when trying to understand the importance of Pharmacovigilance is that the information that is known from the clinical trials performed during the drug development, can be considered as only the extremity of an iceberg when comparing with the information that may be collected once the drug is in the market.

The limitations of clinical trials are due to its limited size, the narrow population, the exclusion of concomitant therapies and diseases and also the short duration of drug exposition. These limitations contrast with the scenario after the drug is marketed, where it is used by large populations and by different patients in conditions not previously studied. This is why post-marketing surveillance and continuous benefit-risk evaluation are needed.

This way, according to the legislation in force, the MAH must ensure that it has an appropriate system of Pharmacovigilance and risk management in place in order to

assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary.(15)

Risk Management System

The risk management system is a set of Pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to MP, including the assessment of the effectiveness of those interventions.(15)
The aim of a risk management system is to ensure that the benefits of a particular medicine exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole.

Risk Management Plan (EU-RMP)

The description of a risk management system should be submitted in the form of an EU-RMP. EU-RMP contains 2 parts:
Part I:

- Safety specifications;
- Pharmacovigilance Plan.

Part II:

- An evaluation of the need for risk minimisation activities;

And if there is a need for additional risk minimisation activities:

- A Risk minimisation plan.

Risk minimisation activities can be divided into those where a reduction in risk is achieved primarily through the provision of information and education and those which seek to control the use of the medicine.
When it is obvious that a risk minimization activity will be needed in post authorization, consideration should be given to piloting the activity during the development phase to see the effectiveness and suitability. When this is done, the outcome should be provided in the risk minimization plan under the appropriate action.(15)

Provision of information

Provision of information to healthcare professionals and/or patients on the specific risks of a product and the measures on how to reduce them is an essential activity of risk management. This provision of information may be confined to information contained within the Summary of Product Characteristics and Package Leaflet (routine risk management) or may be through the use of additional educational material (additional risk management). The need for additional material beyond the Summary of Product Characteristics and Package Leaflet will depend upon the risk and should be considered on a case by case basis. Experts in risk communication should be consulted as appropriate.

Additional Educational Material

The need for additional educational material and the form in which it should be provided will depend upon the specific safety concern. The aim of a specialized educational programme for healthcare professionals and/or patients is to:

- Enhance understanding of the specific risk(s);
- Enhance understanding of measures to reduce either the frequency or severity of adverse reactions;
- Enhance early detection and treatment (if applicable) of an adverse reaction;
- Enhance patient information, awareness and provide information on the need and use of additional precautions.

The educational programme may include but is not limited to the following materials:

- Healthcare professional letters;
- Physician's Guide to prescribing;
- Pharmacist's Guide to dispensing;
- Checklists for assessing comprehension, knowledge, attitudes, and/or desired safety behaviors about the risk(s). These should be tailored to the target audience (e.g. physicians, pharmacists or patients);
- Checklists for actions before prescribing or dispensing;
- Patient information Brochures;
- Specific training programmes

The choice of media may also need to be considered (written, audio or video) as well as the use of drawing/symbols to improve understanding. For medicines where the target population may include a larger proportion of visually impaired patients, the use of Braille or audio media should be given special consideration. Pre-testing materials in the target audience(s) is highly desirable to help ensure good comprehension and acceptance of the communication method and contents. A variety of testing methods such as readability testing, focus groups or surveys could be used.

Specific training programmes may be considered in certain circumstances. However, it is unlikely that prescription/dispensing of the medicine can be limited to people who have undertaken such a programme.

The above educational materials should be in strict compliance with the contents of the SPC and the Patient Information Leaflet and must be agreed with the Competent Authority.(16)

It was in this context that I developed the review of educational materials, for both patients (in the form of a Patient Card) and healthcare professionals (in the form of a brochure with informative content) for a specific product.
This review consisted in checking the translation from English into Portuguese, the evaluation of the conformity with the SPC content, and compliance with the Annex IIB of the Product Information – "Conditions of the Marketing Authorization". It states that "prior to launch of the product in each MS, the MAH shall agree the content and format of the educational material with the NCA. The MAH should ensure that, when placing the Mp in the market, all healthcare professionals who are expected to prescribe product X, are provided with an Educational pack." This chapter of the Product Information also indicates what must be the content of the educational pack, and the key elements for both prescriber and patient materials. Also important when reviewing the educational materials, is the critical analysis of the content so that I could exclude the presence of advertising information in the materials. This need for distinguish educational from advertising materials is a matter I will approach further in the discussion chapter of this report.

The need for this revision is due to the mandatory approval by INFARMED before implementing the materials in Portugal, which demands a local evaluation with focus in some local requirements regarding the content of the materials.

Literature searches

With the aim of searching for Adverse Drug Reactions (ADR) that could possibly be published in literature, the MAHs perform a systematic collection of data through a literature search. As Pharmacovigilance point of contact for several MAHs and many of their products, Eurotrials is responsible for performing these local literature searches. At a certain point of my training I was assigned with the responsibility of performing these searches, both on a daily and weekly basis. I was responsible for a daily search in 2 Portuguese journals and in the INFARMED's website. On a weekly basis, I was responsible for searching also in the "Index de Revistas Médicas Portuguesas" and "Pubmed" websites. If any safety case appears from this search, an evaluation of it must be performed and if relevance is identified, it should be immediately notified to the MAH. During my training period, no case needed to be notified.

Another important activity in the scope of Pharmacovigilance in which I participated was the Annual Training in Pharmacovigilance, more specifically in "Reception of Adverse Drug Reactions/ Safety Information". This annual training session is mandatory for all collaborators from Eurotrials and takes place because Eurotrials have a Department which provides services in this field and is a contact point for the reception of ADR for some MP. This training session is foreseen in the Eurotrials SOPs.

3.8. General Regulatory Consulting

Within the legal context in EU we can distinguish harmonised and non-harmonised legislation. Harmonised legislation comprises areas like Clinical Trials, Manufacturing, Import, Distribution, Advertising and Inspections. In this case, Directives are transposed to national legislation by each MS. Non-harmonised legislation presently involves areas like pharmacies, Health insurance, Health Technology Assessment, Prices and Reimbursement. Regarding these subjects, each MS defines its own legislation according to its experience/system.

It is also in this scope that Eurotrials develop its activities in what concerns general regulatory consulting. The activities performed include general consulting on local requirements regarding different themes like:

- Marketing Authorization Applications;

- Variations type I, II and Administrative;
- MAH transfers;
- Advertising materials revision/notifications;
- Wholesale distribution of MP;
- Price and reimbursement;
- Clinical trials applications.

During my internship I had the opportunity to elaborate answers to the clients' questions in collaboration with the other members of the department. These activities always involve a period of research about the subject in question, in legislation, CA web sites, etc, gathering the most adequate and reliable information to provide. These specific activities are difficult to present in this report, since they constitute companies' strategies regarding products to introduce in market or other activities that can't be disclosed due to confidentiality reasons.

4. Discussion

In this chapter I will present the aspects I found relevant to discuss in the scope of the activities previously described. In general terms, this internship was made up by a vast variety of activities inserted in different matters, due to the multidisciplinary character of regulatory affairs. Because of this, every tasks performed involved previous preparation. The reading of support material concerning the different contents I dealt with was always part of the performance of the activities. This training period preceding the activity itself, contributed to a light delay in its performance. However, in the course of my internship, I noticed a considerable evolution in terms of time spent on each activity, since the training period became no longer necessary. Also, some activities were developed more regularly, leading to a superior level of efficiency and skills acquired concerning mainly some activities than another.

Clinical Trials

As far as CTs are concerned, in my opinion there are some aspects that are worth to be mentioned in this chapter. As I have already mentioned in section 2.1.1., the three entities involved in the regulatory submission of a CT are IINFARMED, CEIC and CNPD. The role of these three entities differs on what aspects they evaluate during the process. INFARMED evaluates the CT in terms of toxicology, safety and quality of the IMP, CEIC evaluates the methodological, ethical and legal aspects, so monitors CT execution in what concerns the ethical aspects and safety of participants, and CNPD evaluates the kind of personal data collected, the way it is collected and the time of preservation of that data, which means that it ensures the confidentiality of the data collected in Portugal.
In section 2.1.1., I mentioned that I would approach the differentiation between the submission to CEIC and INFARMED. Actually, although submission to both entities is usually made in parallel given the similarity between them, there is some information which is exclusively submitted to CEIC, as for example:

- The study site conditions for the CT conduction, regarding infrastructure, equipment and human resources;
- Ethical evaluation, consisting in an ethical opinion elaborated by the National Coordinator which reflects upon the relevance of the CT execution in Portugal.

- Financial aspects: insurances and compensations regarding participants and investigators as also contracts between sponsor/investigators and sites – this information is also submitted to INFARMED but its evaluation is a CEIC's responsibility.

During the process, it must be assured that the information submitted to INFARMED is in accordance with the information submitted to CEIC. In order to achieve that, it is really important to compare and cross the information from the several documents. Does the CT/sponsor/EU legal representative identification match in the different documents? Does the number of participants/sites predicted in the CTA match the number predicted in the financial contracts of each site? Those are questions that must be assessed.
Also, it may happen that INFARMED/CEIC asks for further information and in that case, since the submission was made in parallel to both entities, it must be assured that the updated information is submitted to both CEIC/INFARMED, through a notification of new documents.
Regarding the ICF, the inclusion of national legal requirements was actually a critical step in the conception/adaptation of the document. Additionally, also the kind of language used is a critical issue, since we must not forget that the document is intended to be understood by participants in the CT which might not be familiar with scientific and technical language applicable in this area.

Another critical issue which is nowadays being discussed is the timelines of approval for CTs in Portugal. Although all entities involved comply with the timelines legally defined (up to 60 days by INFARMED; up to 70 days by CEIC; 60-90 days by CNPD), the periods could still be shortened.
We may have an INFARMED approval in 42 days (in average) but for example, some hospitals may take 6 months to approve a CT financial contract, which causes a huge delay in a CT approval in Portugal.(17) This period is too long and is not affordable for the company who wants to develop its product and place it in the market as soon as possible. So this is the reason why Big Pharma are moving CTs to other countries, especially for countries in Eastern Europe, where approvals are faster.(17) To this constraint contributes the absence of conditions that encourage the development of CT in Hospitals, the lack of specific formation and professionals in this sector, the difficulties in obey to the requirements inherent to the Good Clinical Practices, the heavy bureaucracy required in the context of data protection and lengthy of the processes.(18) So the focus should be on

facilitation/obligation to create clinical research sites and also in professional training in research methodologies.(19)

Marketing Authorization Activities

In this topic I will discuss some aspects I consider relevant regarding the marketing authorization related activities.

The most important thing to retain from this step of the discussion is the importance of these activities as MA maintenance activities. During the life-cycle of the MP, in order to keep it healthy, we need to ensure it is controlled and maintained according to the scientific progress and legislation update. In this scope we can emphasize the activities like the variations, transfers and renewals, all of them performed in order to keep the MP in line with regulatory requirements.

Actually, this work is a big challenge since at the time of the performance of any of these activities, we must be conscious about the entire road the MP already passed through. This means, at the time of the submission of a variation, for example, we need to be aware of the number, type, and impact of other variations previously submitted to the Authority and we need to know if they were already approved or not. This is important mostly for variations with impact in the product information (SPC, labels and PIL), because it is necessary to keep the MP dossier the most updated we can.

Another important aspect to discuss at this point is the outsourcing experience I had. During my internship, I had the opportunity to be allocated to a project that consisted in performing a group of Type IA variations regarding a whole portfolio of a Pharmaceutical Company, with the particularity of being in an outsourcing regime. So, for a period of 1 month, I was working in this company facilities, performing all the tasks related to the variations submission. This was a very enriching experience and in this period I was able to retain some important things, as for instance:

- Contact with the pharmaceutical industry perspective that is very different from the perspective of a consultant company, like Eurotrials. In the one hand, in Eurotrials we perform different types of services, for different types of clients, on the other hand, in pharmaceutical industry we are more deeply involved in the management of the portfolio of the company and the tasks performed are more segmented when comparing to the multidisciplinary of a consultant company.

- Contact with other people with different backgrounds, opening the opportunity for learning exchange.
- Contact with other departments besides Regulatory Affairs (Marketing, Sales, Clinical Trials, etc) and seeing how they interact with each other.

Price and Reimbursement Applications

An aspect I considered important to discuss regarding this topic, concerns the applicable legislation. As already mentioned in this report, within the legal context in EU we can distinguish harmonised and non-harmonised legislation. Prices and Reimbursement are included in the group of non-harmonised legislation. So, as far as prices and reimbursement are concerned, each MS defines its own legislation according to its experience/system.
Regarding the Portuguese legislation in force for this matter, I found it particularly difficult to follow given the number of changes regularly introduced and the different aspects I had to take in consideration to obtain a complete overview of the subject.

Advertising of Medicinal Products

Regarding advertising of MP, a matter I find important to discuss is the thin borderline between advertising and scientific information on MP.
The question that most of the times emerge in our heads is whether the supply of scientific information is a way of advertising or not. The inexistence of legal or other kind of criteria that might distinguish the both concepts and at the same time the need to inform the consumer/patient about new therapeutic options, the correct use of MP or about the product characteristics, made of this a controversial topic. In fact, it is difficult to harmonise the duty to inform with the prohibition of promoting.
After all, in the legal framework, what can be considered as information (not advertising) is:

- The product information (particularly the SPC, PIL and Labelling);
- The correspondence needed to answer a specific question about a particular medicinal product, possibly accompanied by material of a non-promotional nature;
- The factual or informative announcements and reference material relating, for example, adverse-reaction warnings as part of general drug precautions, trade

catalogues and price lists, since they include no other information about the product;

- Information relating to human health or diseases, as long as there is no reference, even indirect, to medicinal products.

Additionally, information must be exact, up-to-date, verifiable and sufficiently complete to allow the receiver to make a correct idea of the MP therapeutic value.

As difficult as distinguishing promotion from information, is to distinguish promotion from education. I am referring to this in this topic because I said previously in Pharmacovigilance section, that I would approach further in the discussion the need for distinguish educational from advertising materials.

This way, at the moment of the revision of the educational materials it is important to perform a critical analysis of the content in order to exclude the presence of advertising information on them. Obviously, educational materials cannot be used as promotional, so, it should not include for example, images referring to patients' well-being or healthy patients but can include for instance, images of the patient but with the purpose of exemplify self-administration. Also, it is important to guarantee that the references in the educational materials are those contained in SPC and PIL, and if others are also included, it should be appropriately justified.

In conclusion, this is a very subjective topic given the difficulty in distinguish the different type of actions that is inform, promote and also, educate.

Medical Devices

In the scope of MDs, the critical points I think I should consider are related to the need for resolution of uncertainties and the drug-devices borderline.

Because this legislation is extensive, complex, frequently written in generalized terms and seeks to create an entirely new regulatory system for products that were formerly largely unregulated, difficulties of interpretation or application are bound to arise.(5)

Actually, this is a fact that can be proven given the number of questions raised by clients in what regards strategy to adopt in MD development and confirmed by the fact that no exact answer can be delivered.

One example of those uncertainties is the drug-devices borderline. Difficult borderline questions arise in relation to a significant number of products, particularly whether they are to be classified as medicinal products or as medical devices.

The Commission has issued guidelines on this drug–device borderline issue and the relevant criteria are:

1. The intended purpose of the product, taking into account the way the product is presented.
2. The method by which the principal intended action is achieved. This is crucial in the definition of a MD. Typically, the MD function is fulfilled by physical means (including mechanical action, physical barrier, replacement of, or support to, organs or body functions). The action of a medicinal product is achieved by pharmacological or immunological means or by metabolism.(5)

Pharmacovigilance

As already mentioned early in the State of the art chapter, there are some predicted changes in Pharmacovigilance legislation. In April, I attended to a Webinar one hour session which subject was “Pharmacovigilance New Legislation”. With that session I was able to consolidate my thoughts in this topic. Actually, what is happening is that the New European Legislation (Directive 2010/84/EC and Regulation No. 1235/2010) has considerable implications on the Pharmacovigilance (PV) system of every EU MAH and changes will start to be implemented by July 2012. This legislation change means significant increase in the workload within Pharmacovigilance departments and industry is expecting a 20-30% increase alone in reported cases volume.

This is the main cause for concern since all Pharmacovigilance departments and professionals need to be prepared for the work flow that will increase substantially.

This preparation begins with training sessions like those I have mentioned, where people can change opinions and different perspectives from different points of view (industry perspective, CRO’s perspective, etc.).

In fact, one of the difficulties I found during the last months was to be aware of all information that was released from EMA about this topic. Several documents were published with very important information and fortunately, the Webinar became a positive way to get round that problem of being updated with all information that was released. It gave me a good perspective, yet, being up to date, obviously involves a continuous learning process and reading of all contents released.

5. Conclusion

“Feed a product to keep it healthy”, this is the key message to retain, as far as RA are concerned. This statement reflects the purpose of the entire monitoring cycle of MP. All the activities described in this report constitute the group of MPs’ needs once they are launched in the market.

The importance of Regulatory Affairs is sustained in the fact that pharmaceutical industry is one of the most regulated industries, given the impact that this business has in people’s lives. The pharmaceutical industry ensures the improvement in diseases’ cure and in the answer to the existent medical needs.

In an ever-changing regulatory environment, the role of regulatory affairs professionals is essential to ensure compliance with legislation. So, the Regulatory Affairs departments in collaboration with Competent Authorities cover a vast and diverse range of activities, ensuring that all phases of research, development, manufacturing, submission, revision and marketing authorization of the MP, comply with the legislation in force for each country.

Regarding the objectives I laid down in the beginning of my internship, at this point I must say that they were achieved. I consolidated my understanding of the importance of RA for the development and approval strategy of new MPs, since I was dealing with real life situations and it was visible the impact of all those activities performed in the products life cycle. Also, the every-day contact with legislation in different circumstances gave me an overall picture of the present regulatory framework applicable Europe. This overall picture now is definitely more complete and understood when comparing with that acquired from studying the legislation previously in my degree and master.

In addition to this, the multidisciplinary framework of this area made this internship unpredictable in terms of activities to be performed during those 9 months. This can be considered as a weakness because in fact, at the beginning of the internship, it was not possible to strictly define a plan, since the activities would always depend on clients’ demands. This way, the type and duration of the activities performed was always according to the requests from our clients, resulting in more or less frequent activities and some activities not included at all in the internship.

Finally, in order to conclude my Master Degree in Pharmaceutical Biomedicine, there is no doubt that opting by this on-the-job training was the right decision. This 9 month

experience allowed me to establish the first contact with the employment world and in spite of the training context it prepared me for real life and for real situations in this specific area. Being at this moment working in Eurotrials, as a scientific consultant in the RS&RA department, makes me feel like this mission has been accomplished with success.

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