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Secção Autónoma de Ciências da Saúde

CÁTIA SOFIA SANTOS BATISTA

CURRICULAR TRAINING REPORT: PHARMACEUTICAL INDUSTRY & SPIN-OFF COMPANY

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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 Doutora Vera Dantas Moura, sócia Gerente da TREAT **U**, Lda. e do Professor Doutor Bruno Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

Dedico este trabalho aos meus pais por todo o apoio e carinho que me deram e sem o qual esta etapa não seria alcançável.

O júri

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Palavras-chave

Estágio; Indústria Farmacêutica; Spin-off; Pedidos de Aconselhamento Científico; Plano de desenvolvimento não clínico; Apoio regulamentar; Assistente da Gerência.

Resumo

O presente relatório expõe as atividades desenvolvidas durante o estágio curricular, frequentado na Bluepharma - Indústria Farmacêutica S.A. e na TREAT U, Lda. uma Spin-off da Universidade de Coimbra, no âmbito do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro.

Esta foi uma experiência de 6 meses que teve duas componentes, uma multidisciplinar e outra monodisciplinar, as quais me permitiram desenvolver os conhecimentos e aptidões adquiridas ao longo do curso de mestrado e de as aplicar ao mundo real. Para além do desenvolvimento de competências profissionais, esta experiência possibilitou também a aquisição e desenvolvimento de várias aptidões, quer a nível pessoal como social.

Nos primeiros dois meses desta minha experiência adquiri um conhecimento essencialmente teórico em várias áreas da indústria farmacêutica (financeira, desenvolvimento de negócio, assuntos regulamentares, investigação e desenvolvimento de medicamentos, garantia da qualidade, etc.) através da minha passagem pela Bluepharma. De seguida, na minha experiência de quatro meses na TREAT U, foi-me dada a oportunidade de realizar de forma mais independente, as funções inerentes ao cargo de assistente da gerência, com especial enfoque para atividades de gestão de projeto (incluindo assuntos regulamentares), tais como, apoio na preparação do plano de desenvolvimento não clínico e na preparação do pedido de aconselhamento científico.

Este relatório começa assim por descrever os objectivos do estágio e uma breve descrição das instituições que me acolheram para a sua realização. De seguida, os conhecimentos adquiridos na vertente multidisciplinar do estágio e depois as atividades desenvolvidas no âmbito monodisciplinar. Por fim, apresenta uma análise das dificuldades e desafios encontrados bem como os esforços realizados para os ultrapassar.

Keywords

"On-the-job training"; Pharmaceutical Industry; Spin-off; Scientific Advice Requests; Nonclinical development plan; Regulatory assistance; Assistant Manager.

Abstract

This report outlines the activities undertaken during the curricular training, performed at Bluepharma, Pharmaceutical Industry S.A. and at TREAT U, Lda. a spin-off from the University of Coimbra, within the scope of the Pharmaceutical Biomedicine Master´s course of the University of Aveiro.

This was a 6-month experience that had two components, one multidisciplinary and other monodisciplinary, which allowed me to develop the knowledge and skills acquired throughout the master´s course by applying them on a day-to-day basis in the real world. Beyond of professional skills development, this experience also enabled the acquisition and development of several skills at both personal and social level.

In the first two months of this experience I acquired essentially a theoretical knowledge in several areas of a pharmaceutical industry (financial, business development, regulatory affairs, research and drug development, quality assurance, etc.) through my passage at Bluepharma. Following, in my four months experience at TREAT U, I was given the opportunity to perform more independently, the functions inherent to the position of assistant manager, with special focus on project management activities (including regulatory affairs), such as support in preparation of nonclinical development plan and in the preparation of the scientific advice request.

This report begins with a description of the training objectives and a brief introduction to the host institutions. Then, explains the knowledge acquired in the multidisciplinary experience and furthermore the activities undertaken at a monodisciplinary level. Finally, it presents an analysis of the difficulties and challenges encountered and the efforts made to overcome them.

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Abbreviations List

AdI	*Agência de Inovação*
	Innovation Agency
ANDA	Abbreviated New Drug Application
API	Active Principal Ingredient
AUC	Area under the concentration time curve
BA	Bioavailability
BD	Business Development
BE	Bioequivalence
CDA	Confidentiality Disclosure Agreement
CDP	Clinical Development Plan
CEO	Chief Executive Officer
CEP	Certificate of Suitability
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum plasma concentration
CNC.UC	*Centro de Neurociências e Biologia Celular da Universidade de Coimbra*
	Centre for Neurosciences and Cell biology from the University of Coimbra
COMPETE	*Programa Operacional Factores de Competitividade*
	Operational Programme of Competitiveness Factors
CRO	Contract Research Organization
CTD	Common Technical Document
DMF	Drug Master File
EC	European Commission
EMA	European Medicines Agency
EOP	End-of-Phase
EPAR	European Public Assessment Report
ERDF	European Regional Development Fund
EU	European Union
FDA	Food and Drug Administration
GARC	*Gabinete de Aconselhamento Regulamentar e Científico*
	Regulatory and Scientific Advice Office
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices

HR	Human Resources
ICH	International Conference on Harmonisation
ICH S	International Conference on Harmonisation Safety
IND	Investigational New Drug
INFARMED	*Autoridade Nacional do Medicamento e Produtos de Saúde I.P.*
	National Authority of Medicines and Health Products
IP	Intellectual Property
ISO	International Standards Organisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare Products Regulatory Agency
MSA	Master Service Agreement
MSDS	Material Safety Data Sheet
NDA	New Drug Application
NIF	*Número de identificação fiscal*
	Tax Identification Number
NME	New Molecular Entities
OECD	Organisation for Economic Co-operation and Development
OHSAS	Occupational Health and Safety Advisory Services
Pre-IND	Pre-Investigational New Drug
QbD	Quality by Design
QREN	*Quadro de Referência Estratégica Nacional*
	National Strategic Reference Framework
R&D	Research and Development
RH	Relative Humidity
RSA	Regulatory and Scientific Advice
SAWP	Scientific Advice Working Party
SI I&DT	*Sistema de Incentivos à Investigação e Desenvolvimento Tecnológico*
	System of incentives for research and technological development
SMEs	Small and Medium Enterprises
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
Tmax	Time to maximum plasma concentration
TOC	*Técnico Oficial de Contas*
	Chartered Accountant
TPP	Target Product Profile

USA	United States of America
VAT	Value Added Tax

1. General Introduction

This document reports my curricular internship experience as part of the training program of Master's degree in Pharmaceutical Medicine which was held in two institutions: Bluepharma, Pharmaceutical Industry S.A.; and TREAT U, Lda. a spin-off company from the University of Coimbra that holds a partnership with Bluepharma.
The internship at Bluepharma S.A. occurred in the period between 5th December 2012 and 3th February 2013 (2 months). At TREAT U Lda., my training started in 4th February 2013 and ended in 31th May 2013 (4 months).
This report is organized as follows:

- A general introduction with the training objectives, current state of the art of Pharmaceutical Industries and spin-offs, and a brief characterization of the host institutions.
- A description of the knowledge, skills and experience acquired during my multidisciplinary training and also the specific activities undertaken at a monodisciplinary level.
- A discussion on the outcomes of the curricular training experience, focused on the accomplishment of goals, expectations, challenges and difficulties, and a brief comparative analysis of pharmaceutical industry versus spin-off company experience.
- A conclusion with the most relevant aspects of the training experience.

1.1. "*On-the-job training*" objectives

The initial training plan included a multidisciplinary experience through the various departments of Bluepharma (Administration, Financial and Accounting, Quality Assurance, Drug Research and Development, Regulatory Affairs, Business Development and Pharmaceutical Development), followed by a monodisciplinary experience developed at TREAT U which involved a more specialized work in the administrative, management of incentives system and research & development (R&D) areas.
The aim of my internship at Bluepharma was to develop assistant management skills and acquire an inside knowledge on the different departments of a proficient pharmaceutical company in order to apply the acquired competences to a spin-off enterprise - TREAT U.
The main goals established for my curricular training were:

- To apply theoretical knowledge acquired in the master's course in Pharmaceutical Medicine, enabling a smooth relationship between the output of education and training systems and the contact with real work world;
- To be able to practice autonomously and efficiently assistant manager functions.

The secondary goals were:

- To complement and enhance social, personal and professional skills;

- To develop soft skills in an organizational environment, such as: interpersonal relationships; teamwork; dealing with emerging difficulties; critical attitude development; working contacts network establishment;
- To develop knowledge within an R&D innovative enterprise;
- Train the writing of technical documents.

1.2. Current *state-of-the-art* of Pharmaceutical Industry and "Spin-offs"

Pharmaceutical Industry

Pharmaceutical Industries have been crossing an unfavourable period for the last decade. The patents of blockbuster drugs expiring and the growth of generic market have created great pressure on the industry pipeline. Moreover, the decreased productivity regarding the generation of new chemical entities with a high rate of failure in late stages of development, quite often in Phase 3, is placing a substantial burden on the health-related R&D Industry, owing to the high levels of investment without significant financial return. Furthermore, regulatory demand has also been increasing during pharmaceutical development, through the implementation of tight measures by regulatory authorities.

The profitability of the Pharmaceutical Industry and growth prospects are further threatened by the implementation of cost containment measures of governments for healthcare expenditures (i.e. cut-spending in hospital drugs) (1-3).

To overcome these drawbacks, Pharmaceutical Industries have been changing their business model and finding new solutions in order to keep their revenue rates growing.

A striking feature of industrial innovation today is that only a small minority of firms innovate alone. In the attempt to adapt to an environment of high risks, global competition, increasing cost, complexity of technological advancement, and rapid generation & diffusion of technical knowledge/know-how, a large numbers of firms have selected cooperative relationships as the most viable strategy to increase and maintain their pipeline. This decreases risk of investment on R&D for innovative therapeutic solutions and increases the probability of hitting a blockbuster (1-3).

Spin-offs from Academia

Academic entrepreneurship via university spin-offs is an emerging field of research focusing on the process of generating, discovering and developing innovative opportunities created through university research (4-6).

The onset of university spin-offs has been one of the major trends observed recently in the R&D field and they represent the rise of entrepreneurship as a driver for innovation, competitiveness and economic development (4-6).

Academia spin-offs serve to transform technological breakthroughs from university research, which would probably remain unexploited otherwise, into marketable goods – technology transfer and commercialization. This means that through certain mechanisms

and incentives, universities can bring knowledge developed in R&D activities into the market through the creation of spin-offs (4-6).
New graduates, which decide to become entrepreneurs of spin-offs, may be important channels for disseminating the latest knowledge from academia to the industry. Furthermore, there is a great trend to maintain a cooperative relationship between these spin-off and universities for a continuous knowledge and technology transfer.
In most countries, as is the case of Portugal, universities can claim the intellectual property (IP) rights on technologies developed in their laboratories. Therefore, the process of establishing the spin-off as a new corporation involves transferring the IP to the new corporation or giving the latter a license on this IP (4-6).

Pharmaceutical Industry *versus* Academia spin-offs
The global competitiveness and the rising costs of pharmaceutical R&D are creating great pressure in pharmaceutical industry business.
Therefore, pharmaceutical companies are exploring options to enhance the efficiency of the resources they are using at all stages of the value chain, from discovery research to production and logistics as well as sales and marketing (3, 7, 8).
Companies are increasingly recognising that non-core activities can be performed more effectively by a third party, with lower costs or through direct access to proprietary know-how, while focusing financial and other resources in its core activities.
As a result, the number of cooperative R&D relationships has increased significantly during the last years, and the partnerships between pharmaceutical industries and academic spin-offs follow this trend (3, 7, 8).
Academic spin-offs, with new entrepreneurs emerging from Universities, can offer cutting-edge research and expertise to the Pharmaceutical Industries, enhancing their R&D productivity and providing profitable opportunities. These are very important elements to foster innovation and help companies compete in the global, knowledge-based economy.
Spinning off new ventures from academic laboratories is a valid method of technology transfer and commercialization, which brings benefits to all parties involved (3, 7, 8).

1.3. Host institutions

1.3.1. Bluepharma, S.A.

Bluepharma is a Portuguese capital pharmaceutical company, based in Coimbra, which initiated its activity in February 2001, when a group of experienced professionals bought the state-of-the-art industrial unit from Bayer.
Bluepharma group is divided in Bluepharma, Pharmaceutical Industry S.A. and in Bluepharma Genéricos (Table 1).

Bluepharma, Pharmaceutical Industry S.A. concentrates its efforts in 2 distinct areas:

- The manufacturing and packaging of pharmaceutical drugs for Bluepharma Genéricos (25%) and for other national and international companies (75%);
- The research, development and registration of pharmaceutical drugs, in partnership with other companies.

Bluepharma Genéricos, founded in 2002, is centred in the marketing of generic pharmaceuticals. The high rate of patent expiration for blockbuster drugs in the last years, created great business opportunities for generics companies, and Bluepharma Genéricos has seized this promising market.

Table 1: Activity areas of Bluepharma Group (Source: Bluepharma)

Bluepharma Group		
bluepharma® Indústria Farmacêutica, S.A.		bluepharma® GENÉRICOS
Manufacturing and packaging of pharmaceutical drugs for Bluepharma Genéricos (25%) and for other national and international companies (75%)	**Research & development** and registration of pharmaceutical drugs, in partnership with other companies	**Marketing of Generic Pharmaceuticals**
60,3%	11,2%	28,5%

Despite the substantial investment in the production and commercialisation of generics, other major trend and policy of the company is innovative medicinal products.
Concerning the R&D of pharmaceuticals, Bluepharma is making a strong investment, already recognized by Ministry of Science and Technology. The company has been concentrating its research efforts on emerging areas, namely nanotechnology, oncology and biotechnology, where it has developed a set of partnerships (Figure 1).
These partnerships were intended to produce translational investigation for the development of products with social and economic impact on the healthcare system and to support entrepreneurs with a global market view.
Thus, Bluepharma have been involved in the launch of two new spin-off companies of a technological base, which are devoted to the research on new therapeutic solutions for the cancer treatment – Luzitin S.A. and TREAT U, Lda., both based in Coimbra. Bluepharma also holds 10% of the biotechnological research company Technophage S.A., based in Lisbon.

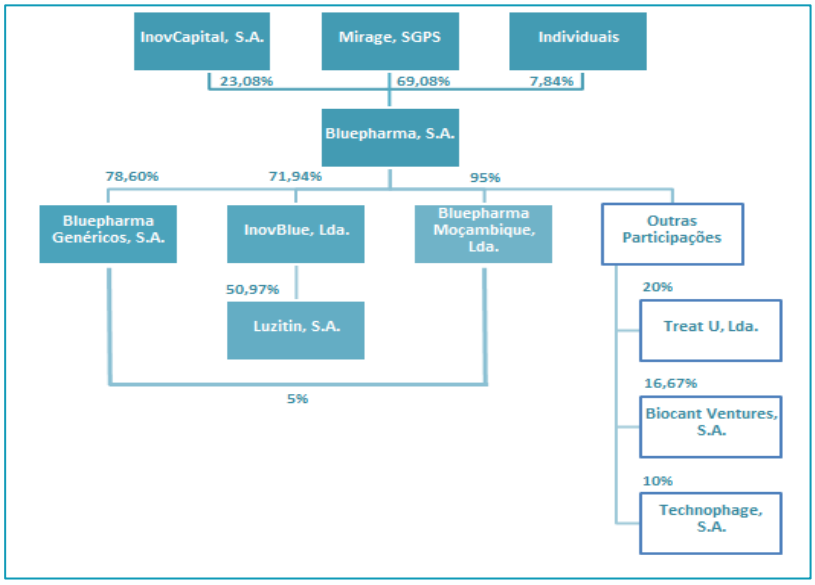

Figure 1: Bluepharma partnerships (Source: Bluepharma)

1.3.2. TREAT U, Lda.

TREAT U is a spin-off company from the University of Coimbra, founded in January 2010 and based in Coimbra. The co-founders are Vera Moura, Sérgio Simões and João Nuno Moreira, entrepreneurs and scientists with a vast experience in the fields of Biotechnology and Pharmaceutical Technology.

The company is part of the innovation network at the National Scientific and Technological System, since it is connected to the Centre for Neurosciences and Cell biology from the University of Coimbra (CNC.UC) and Biocant Park.

Because cancer is a disease where there is still an unmet medical need, TREAT U´s mission is to develop more effective strategies and safer products for the oncologic patient by increasing therapeutic efficacy and reducing the incidence of adverse side effects, hence reducing treatment costs for healthcare systems (end-users) and generating a pipeline of interest for the Pharmaceutical Industry (primary costumers).

TREAT U is dedicated to the development of targeted nanotechnology-based platforms for the specific delivery of drugs in the oncology area. These platforms aim at increasing concentration of the drug in the tumour, and decrease the incidence of side effects by decreasing drug accumulation in healthy organs.

The first product developed by the company was the platform PEGASEMP™.

IP rights of the PEGASEMP™'s are protected by a patent already granted in the United States of America (USA), in July 2012, and currently in evaluation in Europe. This platform was developed at CNC.UC, and a license agreement between TREAT U and the University of Coimbra was already established, granting the commercial rights to the first party on therapeutic and diagnostic applications.

TREAT U has received funding from the National Strategic Reference Framework (QREN) and the partnership held with Bluepharma S.A., a company with a profound knowledge of

the pharmaceutical market and a vast expertise in the development and licensing of technologies and medicines to international markets, has enhanced TREAT U´s management skills and networking.

TREAT U is currently at the scale-up phase (in more detail in section 2.2.1.1.) and planning the nonclinical studies for the PEGASEMP™. Then, the intention is to develop its pipeline until phase IIa clinical testing is concluded with successful evidence of safety and efficacy, and licensing proprietary technology to a Pharmaceutical company, which will conduct the latter stages of clinical trials and commercialisation.

2. "On-the-job training"

In this section, I will contextualise both the general (multidisciplinary) and specific (monodisciplinary) training.

My multidisciplinary experience was acquired in Bluepharma. The two months spent in this company allowed me to gain a general comprehension of the organization and interaction between its several departments, and gather an overview of the activities performed and the interconnection between them. Table 2 summarizes the main responsibilities observed and the acquired knowledge in each department, as well as the duration of the internship. These topics will be developed with more detail in the section 2.1.

Table 2: Internship plan for multidisciplinary experience at Bluepharma

Department	Areas of knowledge development	Person(s) responsible	Duration (Working days)
Administrative	- Communication skills - Press releases - Maintenance of the internet site - Archive organisation - Administrative assistance - Briefing - Annual report - Organisation and assistance of scientific and management meetings (convene procedures, agenda, minutes, etc.)	▪ Ana Luísa Santos	16
Financial and accounting	- Invoices validation - Incentives system and applicable legislation - Management of QREN incentives system	▪ Cesaltina Antunes ▪ André Figueiredo ▪ Andreia Lopes	8
Quality assurance	- Bluepharma´s Quality Management System and guidelines applied for its development	▪ Teresa Murta	4
Non-clinical development	- Non-clinical development plan - Clinical development plan - Nonclinical studies outsourcing	▪ Ana Catarina Pinto	2
Regulatory affairs	- Common Technical document - Management of variations to the terms of a marketing authorisation	▪ Emília Alcoforado ▪ Janete Sousa ▪ Ana Margarida	2
Business development	- Confidentiality disclosure agreements - Intellectual Property rights (i.e. Patents)	▪ André Freitas	1
Pharmaceutical development	- Steps for the pharmaceutical development of a generic medicinal product - Stability studies - Bioavailability and Bioequivalence studies	▪ Sónia Alfar ▪ Rui Saltão ▪ Yara Rocha ▪ Ana Pedro	2
Total of working days			35

My multidisciplinary experience acquired in Bluepharma allowed me to gather important information, in order to export some of this knowledge for TREAT U and perform my tasks as assistant manager. The monodisciplinary activities developed at TREAT U, are outlined chronologically in the table below (Table 3).

Table 3: Chronological distribution of developed activities at TREAT U

Developed activities	February	March	April	May
Administrative support				
Management of the incentives system				
Project management				

2.1. Multidisciplinary training

In this topic I will explain the knowledge acquired in my multidisciplinary training at Bluepharma. Thus, in the following seven sub-sections, I will give an overview of each department and in what way they contributed to my skills and knowledge development. In most of them, the acquired knowledge was mainly theoretical, since no activity was entirely performed.
This experience also allowed me to realize the importance of each department and how they depend on each other's support for the achievement of the management goals and broadly the company´s common goals.

2.1.1. Administration

The Administration department within an organization develops the required tools to accomplish the main goals and mission of that organization.
Henri Fayol describes the "functions" of the administrator as 5 elements (9):

- Planning - deciding in advance what/how/when to do it, and who should do it;
- Organizing - assigning responsibilities to departments and relationships;
- Staffing - screening people to fill the positions and then allocating them properly;
- Controlling - evaluating quality in all areas and detecting deviations;
- Budgeting - implementing of a budget plan.

Bluepharma has currently four managing directors: one Chief executive officer (CEO); one Vice-President and director of operations; one Vice-President and director of business and product development; and a member of the board. Thus, with distinct skills and involved in different areas, they complement themselves.

Bluepharma managing directors have, in their action plans, the support of ten members of the management team and two administrative assistants, to ensure all strategic and operational activities of the company in the fields of innovation, research, business and product development, manufacture, quality, packaging and distribution of medicinal products.

The duration of my internship in administrative department of Bluepharma was about 16 working days.
Ana Luisa Santos, Bluepharma´s board assistant, was responsible for providing me with an overview of the administrative process, which is part of her professional responsibilities.
An assistant to the board must be able to comply with the dynamics of the company and be flexible in managing the distinct functions for which she was admitted.
The aim of my internship in this department was to observe Ana Luísa performing her normal daily functions.
Some of the tasks observed were the following:

- Organisation of events and journeys (i.e. travel plan elaboration for board members);
- Support to affiliated companies (Luzitin and TREAT U);
- Meetings preparation of Board of Directors and General Assembly (i.e. meeting planning and scheduling; agendas; meetings logistic preparation; minutes meetings; etc.);
- Update of the company's communication channels and brand monitoring;
- Organisation of participation in trade fairs and promotional events, as well as advertising materials needed;
- Preparation of press releases;
- Preparation of notices within the company;
- Preparation of graphic materials, programming and web communication;
- Preparation of written content to the various departments;
- Processes and internal communication initiatives to/from the outside – company communication plan;
- Registry and stamping of incoming and outgoing Bluepharma´s correspondence;
- Guided tours to Bluepharma´s facilities provided to journalists;
- Documentation management and archiving;
- Management of back office of Bluepharma website;
- Management of Bluepharma´s identity in the media;
- Exchange of information between employees and board members and back.

In this department I was able to perform the following tasks, under Ana Luísa supervision and support:

- Filling out a form on the website of a carrier (UPS) for the shipment of Bluepharma´s documentation to Italy;
- Development of a travel plan for an employee of Bluepharma (see Annex 1).

This information was extremely useful to the functions and tasks performed later, in monodisciplinary experience, at TREAT U (described in section 2.2. of this report). This approach enabled me to understand the dynamics and the multidisciplinary functions that an administrative assistant shall provide to the management team.

2.1.2. Financial and accounting: management of incentives systems

Among the various roles that a financial and accounting department plays within a company, the major one that stands out is the management of the company budget. This budget could come from operational profits, ventures capital, partnerships establishment, investors, and other earnings. More recently, European initiatives have emerged aiming to improve economic growth and innovation in European countries, through funding.

In pursuit of its strategy for internationalization and diversification of markets, Bluepharma has defined a vast investment program for the period 2009-2012, through the QREN programme. Bluepharma has the support granted under the QREN incentive systems for the "development of dynamic competitiveness factors at small and medium enterprises (SMEs)" and "manufacturing innovation". The most relevant and complex areas for investment are Production, Quality Control and Training analysis. Bluepharma also benefits from an incentive system in co-promotion[1] with Luzitin.
Bluepharma´s financing and accounting department is the responsible for the management of this incentives (co-founding) provided by QREN to the company.

In the description of the activities of financial and accounting department I will focus only in the way it manages the funding systems provided by QREN to Bluepharma and Luzitin. This because, my quick passage through this department was with the objective of learning more about this management process and applicable legislation, for afterwards allowing me to perform the tasks required, at TREAT U (also supported by QREN funds).
Therefore, I will start by contextualising the source and aim of these financial supports.

National Strategic Reference Framework
The European Regional Development Fund (ERDF) grants the QREN funds, which are intended for the public economic stimulation policies, especially in the promotion of innovation and regional development. These systems of incentives applied to the companies started in 2007 and will end in this year of 2013.
The QREN established a deep reform of the incentive-oriented systems for business investment to ensure greater selectivity in its management and with the objective of focusing on the priorities defined for a sustained economic growth in innovation and

[1] **Projects in co-promotion**, are projects carried out in partnership between companies or between these entities and the scientific and technological system (research and development non-profit organisations included in Portuguese Status sectors, and in superior education institutions) (12).

knowledge. With that purpose three systems of incentives of transversal base were established, according to the project to be supported:

a) System of incentives for research and technological development (SI I&DT);
b) System of incentives for innovation (SI Innovation);
c) System of incentives to the qualification and internationalization of SMEs (SI qualification of SMEs).

Thus, the types of investment projects eligible for support under the incentives systems are (10):

a) R&D companies, including activities for divulgation and activities for increasing earnings, encouraging cooperation in conjunction with institutions in the scientific and technological system, and with other companies and entities;
b) Manufacturing innovation (i.e.: significant improvements to current production; creation of units or production lines with a substantial impact on output, exports and employment; expansion of manufacturing capacities in sectors with high technological content; process, organizational and marketing innovation; favouring the creation of technology-based companies; etc.);
c) Development of dynamic competitiveness factors at SMEs in fields such as: organization and management; development and engineering of products and processes; environment; certification of quality systems; innovation management; integration and training of human resources; etc.

In the QREN, the strategy on incentives for business investment is achieved through the intervention of the Operational Programme of Competitiveness factors (COMPETE) and the mainland's regional operational programmes.

The COMPETE programme, approved on 5 October 2007, is part of the QREN, and its aim is the sustained improvement in the competitiveness of the Portuguese economy in a global market context. The COMPETE Management Authority is responsible for managing and executing this programme (11).

COMPETE intervenes in strategic dimensions, such as innovation, scientific and technological development, internationalisation, entrepreneurship and the modernisation of the public administration. Its main objectives are (11):

- To foster an innovation- and knowledge-based economy by stimulating scientific and technological development and encouraging entrepreneurship;
- To improve qualifications in the production sector by upgrading specialisation profiles and business models;
- To stimulate orientation towards international markets on the part of the Portuguese economy by increasing production suitable for trading or internationalisation;
- To qualify the public administration and make state action more efficient through modernisation and the promotion of a public service culture focused on citizens and companies.

The instruments to achieve these objectives are: company investment incentive schemes; financial engineering mechanisms; and collective actions to build the capacity of the national science and technology system (11).

Incentives systems - Applicable Legislation

The Decree-Law No. 287/2007 of August 17 (10) approved the national framework of incentives for business investment, which outlines the conditions and rules to be observed by the applicable business-investment incentive systems on the mainland (10).

However, within the context of the overall plan aimed at boosting European economic recovery, in response to the current economic and financial crisis, the Portuguese government presented a package of measures, including implementation of flexible terms and conditions to be adopted in QREN incentive systems whose enactment is intended to revitalize the support of business and economic activity by stimulating investment and employment.

Thus, Decree-Law No. 65/2009 of March 20 has made some changes to the classification of business investment incentive systems on the QREN Competitiveness agenda, regulated by Decree-Law No. 287/2007, to adjust them to the current international economic reality, and to strengthen them as stimulus instruments for investment and job creation, particularly in the fields of innovation, globalization, and research and development (10, 12, 13).

The duration of my internship in the financial and accounting department of Bluepharma was of 8 working days and allowed me to acquire the knowledge related to the QREN incentives and become familiar with the tools for this funding management, which would later be applied to TREAT U (also an SI I&DT in co-promotion). Therefore the description of the knowledge acquired here focus only in this field.

Cesaltina Antunes, Bluepharma´s chartered accountant (TOC), André Figueiredo and Andreia Lopes, accountants, were responsible for providing me with an overview about the management of the incentives provided to the company.

I was given the following tasks to perform in the first three days:

- To become acquainted with the website of the QREN/COMPETE (http://www.pofc.qren.pt/). In this website it is possible to check all information about the incentives program. Here we can find, for example: open and closed contests; application forms; reimbursement request form (for download); applicable legislation; technical and management guidance's, and so on.
- To compile in a file and read all the legislation applicable to QREN:
    - Decree-Law n. º 287/2007 of August 17
    - Ordinance n. º 1462/2007 of November 15
    - Ordinance n. º 711/2008 of June 31
    - Decree-Law n. º 65/2009 of March 20
    - Ordinance n. º 353-B/2009 of April 3
    - Ordinance n. º 1102/2010 of October 25

After reading this legislation, Cesaltina Antunes made me several questions to make sure I had understood its contents and if I would be able to apply them in practice.

In the fourth day, André Figueiredo provided me some information about how to validate an invoice. This is an important task, because when an invoice is submitted for reimbursement through the incentive system, it must be valid, otherwise will be rejected

(not reimbursed). Thus, in order to confirm if an invoice is valid we should verify the following:

- That it contains the explicit designation of Invoice;
- Contains the correct address and tax identification number (NIF) of our company;
- If the NIF (for Portuguese companies) or value added tax (VAT) identification number (in case of the foreign invoices) are valid and correspond to the supplier. This confirmation should done through the consult of:
    - The Portuguese Ministry of finance website: http://www.portaldasfinancas.gov.pt/pt/main.jsp?body=/external/slelei/SLELEI/listaLeiloes.htm, for NIF confirmation of National invoices,
    - European Commission (EC) website for VAT validation: http://ec.europa.eu/taxation_customs/vies/?locale=pt, concerning European invoices.

After this theoretical information about invoice validation, André Figueiredo gave me several invoices in order to confirm if these were valid according to the parameters mentioned in the topics above, including website consultation for NIF and VAT validation.
Afterwards, from the 5th to 8th day, I was with Andreia Lopes, person responsible for the management of QREN incentives granted to Bluepharma.
With Andreia Lopes I had the opportunity to observe her work and gather the necessary information about this process to further apply in my monodisciplinary experience. She explained to me how to handle with the payment (reimbursement) request form, available in the website of COMPETE, for reimbursement applications.
Beyond observing her filling and submitting reimbursement requests, I also had the opportunity to fill some reimbursement request forms with the invoices information (i.e. date; invoice number; type of expenditure; value paid; etc.) to practice a little.
This process is explained in further detail in the monodisciplinary training part of this report (section 2.2.).

2.1.3. Quality assurance

The quality of pharmaceuticals is a concern for all regulatory entities. Quality assurance enhances companies' success by ensuring the quality and the safety of the pharmaceuticals developed and/or produced. Quality assurance for pharmaceuticals can be divided into major areas: development, quality control, production, distribution, and inspections (14).

In 2003, Bluepharma gathered combined certifications in International Standards Organisation (ISO) 9001/2000 (for quality), ISO 14001/1999 (for environment), and Occupational Health and Safety Advisory Services (OHSAS) 18000 (for safety and occupational health).
Thus, Bluepharma is committed to ensuring the quality of manufactured and distributed medicinal products, to respecting the environment as well as safeguarding the working

conditions of its employees, through the implementation of a quality, environment, health and safety system. Bluepharma is also Good Manufacturing Practices (GMP) certified by the National Authority of Medicines and Health Products (INFARMED I.P.). The scope of their certification is on research, development, innovation, manufacturing, licencing and commercialisation of pharmaceuticals.
These policies are feasible through individual- and team-work, which focuses on defining, revising, approving and implementing new and more ambitious goals concerning to quality, environment and occupational health and safety.
As a certified company, Bluepharma has a Pharmaceutical Quality System implemented. This system requires the definition of policies, procedures, specifications and norms for the activities performed in the company. This documentation is hierarchized according to activities description specificity (Figure 2).

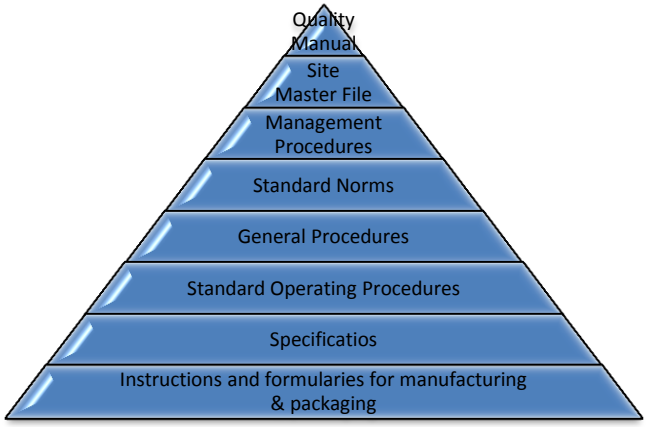

Figure 2: Documentation hierarchy of Bluepharma´s Quality System (Source Bluepharma)

The duration of my internship in the quality assurance department of Bluepharma was of 4 working days.
The head of quality assurance, Teresa Murta, was responsible for providing me an overview about the documentation used to support the preparation of these standards and procedures. Thus, the support documents that should be consulted when preparing such procedures are the following: International Conference on Harmonisation (ICH) Q9 and Q10 quality guidelines; EC EudraLex - Volume 4 for GMP guidelines; ICH Q7; Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) parts 210 and 211; and guidance's for ISO 9001 and 14001.
During my internship in this department I had the opportunity of consulting some Bluepharma´s procedures/norms of the quality management system.
I started by reading the "Documentation System" standard norm (NP-04), in order to understand how the documentation is hierarchized:

- The Quality manual describes Bluepharma´s commitment to meet the requirements of ISO and OHSAS norms, GMP´s and other applicable legislation. This manual also describes the company organization and management responsibilities;

- The Site Master File has a description of all company´s operations, and was compiled based on Eudralex vol. 4, part III;
- The Management Procedures describe in a general manner, how company's commitments are ensured in the context of the quality management system and refers to other document levels that indicate in more detail how to perform each activity;
- The Standard Norms are standards of general scope based on quality elements applicable to all activities related to all departments;
- General procedure, are related with the standard norms, but more detailed. These describe in a broad sense the mechanism how each department should conduct its activities. Thus, serve as the basis for drawing the standard operating procedures (SOP)´s for each department;
- SOP´s determine with specificity the execution of each task of each sector;
- The specifications describe in detail, the requirements that the products/materials used or obtained in the manufacturing process should fulfil;
- The instructions and formularies for manufacturing and packaging cover, for example, manufacturing registries, packaging registries, laboratory diaries, etc.

When some of these documents need to be changed, for improvement reasons, an amendment request must be submitted to the quality assurance department, and the standard norm for Changes Management (which I had the opportunity to read) should be followed.

Beyond reading the Quality Manual and the Site Master File, I had the opportunity of reading some other general procedures and standard norms applicable to the company, namely: Standard Norm for personnel qualification and training; Standard Norm for the management of standard deviations (non-compliance with established standards); and the General Procedure for Quality Risk Management (a process for the assessment, control, communication and review of risks to the quality of the medicinal product across its lifecycle), based on guideline ICH Q9.

In this department, I realized that in addition to following the procedures, another important concept for a certified company is that everything that is done must be properly registered –"*which is not registered, it was not done*".

Within this department, I still had the opportunity to have contact with other professionals (Carolina Ribeiro and Maria João Pereira) with experience in the quality assurance of the manufacturing and packaging procedures. They provided me the opportunity to observe their activities while working, specifically, in the verification and quality assurance of production and packaging registries.

Furthermore, I had the opportunity to attend an education session about "Good Manufacturing Practices", provided by Margarida Carvalho, head of Quality Management, to Bluepharma´s new employees.

2.1.4. Drug research & development

The drug R&D process can be divided into a number of distinct stages, which may overlap in time. Typically the process starts with basic discovery activities. The discovery phase often involves thousands (about ten thousand) of new molecular entities (NME's) being screened for activity against a target disease. The successful NME´s that went through subsequent stages are then checked for their potential toxic effects, again in screening-type tests, further reducing the number of potential drug substances taken forward to full development (15).
Hence, the different steps in classical drug lifecycle are characterised by four well-defined stages: NME research and discovery; Nonclinical development (in animals/*in vitro*); Clinical development (in humans); Phase IV or post-marketing studies. All these phases are properly regulated, so that the product complies with all necessary requirements during its whole development (15).
The first stage, the discovery of a potential NME, is not covered by a regulatory standard, nor are studies that demonstrate proof-of-concept (e.g. preliminary pharmacological studies not designed to test safety).
In the second stage – Nonclinical development –, it is required to conduct the studies under good laboratory practices (GLP) conditions. The primary purpose of these studies is safety testing. Toxicology and safety pharmacology studies, with a potential extension to pharmacokinetics and bioavailability, are those were compliance with GLP is required.
In the third stage – Clinical studies – good clinical practice (GCP) is the basic requirement for quality standards, ethical conduct and regulatory compliance. GCP must be instituted in all clinical trials from Phase I to Phase III.
The fourth stage is post-approval. Here, the drug has already been registered and is available on the market. However, even after marketing approval, the use of the drug is monitored through formal pharmacovigilance and risk management procedures. Any subsequent clinical trials must also comply with GCP.
From stage three of development and continuing throughout the rest of the drug's lifecycle, GMP applies to all manufacturing of active pharmaceutical ingredients (API) and formulated medicines (15).

Concerning the R&D of pharmaceuticals, Bluepharma has been concentrating its research efforts on emerging areas, namely nanotechnology, oncology and biotechnology, where it has developed a set of partnerships.
From an R&D partnership between Bluepharma and the University of Coimbra emerged a spin-off company - Luzitin S.A.. The company is currently working on the development of a family of patented photosensitizer compounds with proven antitumor activity in the Photodynamic Therapy.
Therefore, the knowledge I acquired in the R&D department was through Luzitin´s experience.

The duration of my internship in the R&D department of Bluepharma was of 2 days.

Ana Catarina Pinto, head of nonclinical development at Luzitin, was responsible to provide me a theoretical overview about the way that nonclinical and clinical development plans are prepared concerning innovative drugs, and aspects related to the outsourcing of nonclinical studies to contract research organisations (CROs). This information enabled me to complement the knowledge acquired during the master´s course.
Therefore, I will present in more detail the contents addressed on:

I. Nonclinical development plan – guidelines and principles applied for its preparation
II. Clinical development plan (CDP)
III. Outsourcing of nonclinical studies to CROs

I. Nonclinical development plan

Aimed at a suitable preparation of the nonclinical development plan, Ana Catarina has alerted me for the importance of a previous evaluation of the competitor products already commercialised or under review process (their strengths and weaknesses). Reliable information about competitors is usually available in the European Medicines Agency (EMA)´s and FDA´s websites and also in peer-reviewed scientific articles. Through EMA´s website it is possible to consult the summary of product characteristics (SmPC), scientific discussions, and the full scientific assessment report called a European public assessment report (EPAR) for every authorised medicine. FDA also provides in its website (http://www.accessdata.fda.gov/) reviews of approval processes.
For the conduct of nonclinical studies in GLP conditions, Bluepharma adopted the outsourcing scheme.
The scope of nonclinical studies, GLP principles, and the guidelines applied for the development of a nonclinical plan are explained in detail in the section 2.2.1.3.

II. Clinical development plan

A clinical trial is just one piece of the complex puzzle of drug development and its proper planning is crucial to obtain later on marketing authorisation.
The elaboration of the CDP is intended to compile all the information necessary for the proper conduct of clinical trials, in order to accomplish the objectives. CDP is useful to provide guidance to the project team and helps them to get committed to the goals of the studies.
Beyond the multidisciplinary discussion and interaction within the company, the definition of a CDP requires interaction with the outside world. In addition to the regulatory authorities, it may be necessary the opinion of medical or scientific consultants specialized in the treatment, research centres, etc.
Depending on the complexity of the project the writing of a CDP can take between 3 to 6 months. The first version of the document should be available at least before recruitment of patients. However, some companies (especially larger ones) prepare CDP earlier (i.e., before the first study in man). A CDP is a live document, which means that should be

regularly updated in order to improve the productivity and efficiency of the development process (16).

For the development of the CDP, it is very important to be aware of the different phases that make up the clinical trials, each with well-defined milestones and deliverables, and how they should be planned (study design). For this reason, I will provide an overview of these different phases, their purpose and typical designs.

Clinical drug development can be classified in four phases (Phase I-IV), according to when the study occurs during clinical development (Figure 3). However, it is important to say that the temporal phases do not imply a fixed order of studies.

Phase I starts with the initial administration of an investigational new drug (IND) into humans. Human pharmacology studies are normally identified with this phase; however, they may also be indicated at other points in the development sequence, as shown in Figure 3. Studies in this phase of development are generally conducted in healthy volunteers (with non-therapeutic purposes) in order to test safety. However, for drugs with significant potential toxicity (i.e. cytotoxic drugs), they are usually studied in patients with the target disease. The design of the studies of phase I can be: open label (controlled or uncontrolled); or blinding and randomised, to improve the validity of observations. Studies conducted in Phase I usually involve one or a combination of the following aspects: estimation of initial safety and tolerability for latter clinical studies (typically with both single and multiple dose administrations of the drug); pharmacokinetics (particularly important to assess the clearance of the drug and to anticipate possible accumulation of metabolites); assessment of pharmacodynamics; and some preliminary studies of activity or potential therapeutic for the drug (17).

Phase II, typically involving initial therapeutic exploratory studies, has the primary objective of exploring therapeutic efficacy in patients. These studies may use a variety of study designs. Initially, include concurrent controls and comparisons with baseline status, to give an early estimate of dose response. Subsequent trials are usually randomised and concurrently controlled to evaluate the efficacy of the drug and its safety for the therapeutic indication. Studies in Phase II are typically conducted in a relatively homogeneous population, since the group of patients are selected by relatively narrow criteria. Phase II studies are intended to determine the dose and regimen for Phase III (17).

Phase III studies, are intended to demonstrate, or confirm that a drug is safe and effective for use in the intended indication and in the target population - therapeutic confirmatory. These studies further explore the dose-response relationship, or explore the drug's use in wider populations, in different stages of disease, or in combination with another drug (especially for drugs intended to be administered for long periods). They are intended to provide an adequate basis for marketing approval (17).

Phase IV initiates after drug approval. It is intended to study the effects of the drug on a day-by-day basis and detect rare adverse effects or drug-drug interactions. They are not considered necessary for approval but are important for optimising the drug's use (17).

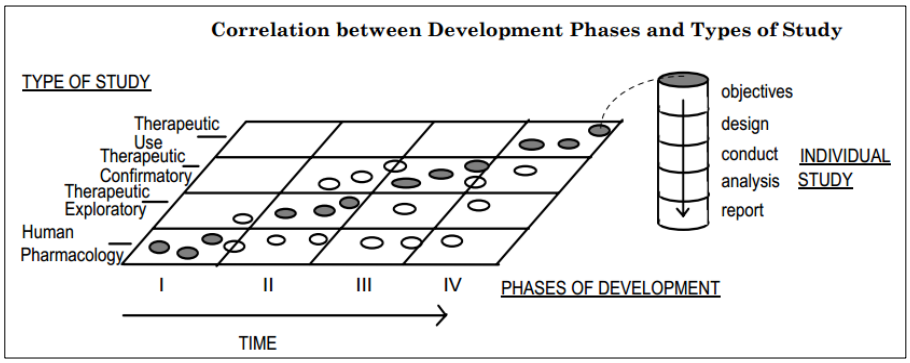

Figure 3: Correlation between phases of drug development and type of clinical study (17)

To initiate the preparation of CDP it is crucial to understand the documentation that should be accessed. Ana Catarina Pinto has alerted me for the importance of generating checklists with the sources that should be consulted in order to gather the necessary information for the preparation of the CDP. This aims at providing the maximum of information and facilitates and accelerates the research. The sources to which I refer above, include the ones that have information concerning:

- The disease - epidemiological information, diagnosis, target population, etc., - provided in medical literature, expert opinions, recent peer-reviewed articles, or by Associations or Society´s of the disease (i.e. American Cancer Society; American Association for Cancer Research);
- Approved products for the target disease (if any) – same sources (updated) as indicated above for nonclinical development (i.e. EPARs´; SmPC; etc.);
- Competitors under discovery or nonclinical development phases, i.e. papers;
- On-going/completed/terminated clinical trials (i.e., at www.clinicaltrials.gov) for similar products;
- Requirements applied for the proper design of clinical trials – i.e., guidelines (ICH, EMA, FDA, etc.).

Clinical trials should be conducted in accordance with the ICH E – Efficacy – guidelines, thus, in order to properly fill the CDP, these should be followed.
ICH E6R1 guideline on GCP it is the general standard for the conduct of clinical trials. "*GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible*" (18).
The aim of ICH GCP guideline is to provide unified standards for the EU, Japan and USA, in order to facilitate the mutual acceptance of clinical data by the regulatory authorities of these regions at the time of its submission for marketing authorisation (18).

The organisation and contents of a CDP are established within the company internal requirements.

Ana Catarina Pinto provided me two examples for possible structures of a CDP (Tables 4 and 5).

Table 4: Example of a CDP structure (Source: Luzitin).

1. Disease definition and contextualisation
2. Epidemiology
3. Main clinical features and diagnosis
4. Therapeutic approaches
    4.1. Historical perspective
    4.2. Current therapeutic options and guidelines
    4.3. Therapeutic trends
5. Similar products approved and marketed for the disease
6. Clinical development plan (phase I, II and III)
7. Similar products currently in development

Table 5: Example of a CDP structure (Source: Luzitin)

1. Introduction
    - Information about the therapeutic area (morbidity/mortality)
    - Therapeutics available and limitations/possibility for improvement
    - Strengths and weaknesses of the products available
2. Information about the new pharmaceutical
    - Available data from preclinical and clinical studies (if any)
    - Strengths, weaknesses, opportunities and threats – SWOT analysis – for the product under development
3. Indications and proposed labelling
    - This section may be organized in a tabular form with two columns (one for the information already available about the product and another one presenting the SmPC ideal)
4. Regulatory requirements
    - Specific requirements applicable for the product in development, according to the countries where it is intended to be placed in the market
5. Primary endpoints
    - It is important the early establishment of efficacy endpoints in order to guide the study and for the monitoring of the consistency of the results incoming form the various phases of the studies performed. Some examples of these endpoints are: endpoints for clinical benefit; and social-economic endpoints. Other critical endpoints are the strategy definition for the dose and posology.
6. Plan for clinical phases (I, II, III and IV)
    In this paragraph should be defined by each phase: the objectives, study design, number of patients, treatment assignment, etc.
7. Investigational products
    Include an estimate of the amount of product (experimental, comparators and placebo) needed, and other necessary goods.
8. Timetable (Gantt-chart)
9. Budget
10. Resources (human resources, CRO´s)
11. References
12. Appendix (i.e. guidelines, SmPC of competitors/related products)

III. Contract Research Organisations for nonclinical development

There are many considerations that should be taken into account when selecting CRO´s to be hired for performing nonclinical studies. Ana Catarina Pinto provided me with some, such as:

- Geographical proximity of facilities;
- Range of support services provided within what is needed;
- Experience in the development of similar products;
- Suitability of facilities, equipment and reagents/resources required to conduct the study in question;
- Scientific know-how and experience of the technical personnel with the methods involved in the study;
- Availability of time to dedicate to our project;
- Reputation of the CRO, particularly how they are regarded by regulatory authorities (labs or CROs with history of significant adverse findings resulting from inspections by the regulatory authorities, should be avoided);
- Confidentiality compliance;
- The facility should comply with GLP requirements;
- SOP´s implemented for the proper conduct of the tasks required and to ensure quality and reliability of the results;
- The determination of the cost-value equation offered by labs and CROs being considered for use in the nonclinical program.

It is important to gather these information's from CROs in order to evaluate and compare different proposals and weigh the pros and cons of each.

Other important aspects that should be taken into consideration during negotiation are:

- The establishment of confidentiality disclosure agreements (CDAs)(concept further explained at section 2.1.6. of this report) – important tools to make an initial request for quotation whilst maintaining confidentiality;
- The information that could be revealed and information whose disclosure should be avoided;
- Every aspects contained in the quotation and those that are omitted.

Ana Catarina provided me the crucial steps for an appropriate selection and monitoring of a service provider for nonclinical studies:

1. Identification of prospective nonclinical service providers
    1.1. Definition of the services intended to be requested
    1.2. Identification of putative service providers
    1.3. Signature of Confidentiality and/or Master Service Agreements (MSA) [2]
2. Selection of a nonclinical service provider
    2.1. Request for proposal

[2] Master Service Agreement is a legally-binding contract between two or more parties (i.e. a client and a supplier), governing the contractual relationship between them and providing a framework for the services provided (Government of Canada. Guideline on Service Agreements: Essential Elements, Treasury Board of Canada Secretariat. Website: http://www.tbs-sct.gc.ca/pol/doc-eng.aspx?id=25761&section=text; 2013, 17 July).

2.2. Proposals evaluation and comparison
2.3. Pre-study qualification site visit (before signing the contract)
2.4. Service provider selection
2.5. Study contract signature
2.6. Study beginning

3. Monitoring and evaluation of a nonclinical service provider
3.1. Monitoring and/or site audit
3.2. Reporting following study completion
3.3. Service provider performance assessment following study completion
3.4. Archiving (must be ensured that the service provider will be responsible for the proper archiving of study related documentation for at least 1 year and then delivered to the sponsor).

This information was extremely useful to the functions and tasks performed later in monodisciplinary experience at TREAT U (described in section 2.2. of this report).

2.1.5. Regulatory affairs

Pharmaceutical products are subject to regulations designed by governments to protect public health. The regulatory affairs departments of pharmaceutical companies ensure compliance with all of the regulations and laws concerning their products.
The Regulatory Affairs department is an important part of the organisational structure of pharmaceutical companies. It is involved in every stage of development of new medicinal products from early on, by integrating regulatory principles and by preparing and submitting the relevant regulatory dossiers to health authorities, and in the post-marketing activities with authorised medicinal products.
At the late stage of product development, regulatory professionals are responsible for the submission of the registration dossier - Marketing Authorisation Applications (MAA) in the European Union (EU) or New Drug Applications (NDA) in the USA. It is their responsibility to provide the strategic regulatory framework for the submission, to advise on procedures and formats, to collect, evaluate and compile the scientific data and information on the product. Regulatory affairs officers are the crucial link between their company, its products and regulatory authorities, by managing the communication and negotiations between the parts.
Due to constantly increasing regulatory obligations and new requirements as well as the globalization of the pharmaceutical market, the demands and responsibilities of regulatory departments is becoming more and more complex (19).

The regulatory affairs department at Bluepharma is responsible for ensuring compliance with all of the regulations and laws concerning generic medicinal products, either in development or already approved.

The duration of my path in this department was 2 days. These enabled me to get a general perspective of what is performed here and its importance to the overall activity of the company.

In the first day, Emília Alcoforado, head of regulatory affairs department, provided me with an overview about the tasks performed there, as a way of introduction. The main responsibilities of the regulatory affairs department in Bluepharma are:

- Preparation of the dossier for MAA and submission;
- Compilation of dossiers according to Common Technical Document (CTD) standards (mainly module 3);
- Management of the variations to the terms of marketing authorisation according to the Commission Regulation (EC) No 1234/2008 and the EC Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01);
- Technical writing of the Drug Master File (DMF)[3];
- Assurance of the quality of the API´s provided by the manufacturer. Thus, the manufacturer should submit the support documentation which proves that fills the obligatory requirements:
    - Manufacturing authorisation;
    - GMP compliance certificate, granted by an European authority (even if not European);
    - API Master File, to fill the section 3.2.S of the CTD;
    - Certificate of suitability (CEP)[4] of the API;
    - Audit reports, with a declaration signed by the Qualified Person.
- Ensure regulatory compliance for the manufactured finished products by:
    - Assuring GMP compliance;
    - Compliance with FDA, INFARMED I.P., and EMA requirements and providing all the required documentation during its audits;
    - Enabling customer's audits.

After this theoretical overview of regulatory affairs department activities in Bluepharma, Emília Alcoforado led me to Janete Sousa, with experience in CTD compilation for generic medicinal products[5] in order to provide me more information about this procedure and the guidelines applied. Before describing the knowledge acquired about CTD, I will first contextualise their scope, content and structure.

[3] A **Drug Master File** is a dossier containing information, usually concerning the Chemistry, Manufacturing and Controls of a component of a drug product, to permit the regulators to review this information in support of a third party's submission. There are four types of DMF´s: Type II – drug substance, drug product, intermediates and material used in their manufacture; type III – packaging; type IV – excipients; type V – other sterile manufacturing plants, and biotech (FDA).

[4] The role of **Certification of Suitability** is to confirm the compliance of a material with the requirements laid down in the relevant monograph of the European Pharmacopoeia. Active pharmaceutical ingredients for which a CEP has been granted are suitable for use in medicinal products. This certificate is granted by the Certification Secretariat of the European Directorate for the Quality of Medicines (EDQM site: http://www.edqm.eu/en/certification-background-77.html, 2013)

[5] A "**generic medicinal product** is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy" (21).

The CTD is a document intended to compile all the information and documentation concerning the development of pharmaceutical in a common format, for applications that will be submitted to regulatory authorities. This common format for the technical documentation, will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals, will ease the preparation of electronic submissions and will facilitate the regulatory review process. The ICH M4 guideline presents the overall organisation of the CTD according to the agreed common format (20).

The CTD assembles all the quality, safety and efficacy information of the pharmaceutical product and it is organised into five modules (Figure 4). Whereas Module 1 is region specific, Modules 2, 3, 4 and 5 are intended to be common for all regions (20).

Module 1 is called region specific since contain documents specific to each region (i.e. proposed label for use in the region) and contains regional and administrative information. The relevant regulatory authorities can specify Module 1 content and format.

Module 2 includes CTD summaries. This module should begin with a general introduction to the pharmaceutical product (including its pharmacologic class, mode of action, and proposed clinical use), and then, include the following sections: quality overall summary; nonclinical overview; clinical overview; nonclinical written and tabulated summaries; and a clinical summary. The guidelines to be applied in the organisation of these summaries are: ICH M4Q, M4S, and M4E (20).

Module 3 concerns quality information of the medicinal product. Guideline ICH M4Q provides the recommended structure to present such information (20).

Module 4 includes the nonclinical study reports, and should be organised according the guideline ICH M4S (20).

Module 5 includes the clinical study reports. The information for this module should be presented in the order described in guideline ICH M4E.

In July 2003, the CTD became the mandatory format for MAAs in the EU, in Japan, and the strongly recommended format of choice for NDAs submitted to the FDA, in USA (20).

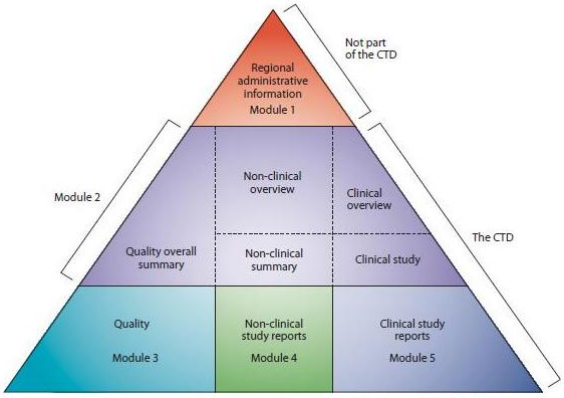

Figure 4: CTD structure - Triangle (Source: ICH M4R3)(20)

Generic drug applications, according to Article 10(1) of Directive 2001/83/EC (21), are not required to provide the results of pre-clinical and clinical trials. Instead, generic applicants must demonstrate that their product is bioequivalent (concept further explained in section 2.1.7.) when compared to the reference medicinal product (a medicinal product for which has been granted a marketing authorisation by a Member State or by the Commission) authorised for not less than 8 years. Generic drug application refers to information that is contained in the dossier of the authorisation of the reference product, since some of this information is not available in the public domain. Therefore, authorisations for generic medicinal products are linked to the 'original' authorisation (21).

Generic drug applications, when submitted to FDA, are termed abbreviated new drug application (ANDA).

Hence, if information on preclinical and clinical trials is not required for generic medicinal products applications, module 2 (with exception of the quality overall summary), 4 and 5 of the CTD need not to be compiled by the generic applicant.

ICH M4 Q(R1) guideline should be followed for compilation of the Module 3 (quality) of the CTD for generics application. According to this guideline, the Module 3 should contain the following major sections (22):

- 3.1. Table of contents of module 3
- 3.2. Body of data
    - 3.2.S Drug substance (name, manufacturer)
    - 3.2.P Drug product (name, dosage form)
    - 3.2.A Appendices
    - 3.2.R Regional information
- 3.3 Literature references

For the reasons described above, the information provided by Janete Sousa, concerning CTD compilation was focused in Module 3 of the CTD, since Bluepharma has only submitted marketing application for generics.

Concerning the **drug substance section** (3.2.S of the CTD), the information used to fill it is based on API master file provided by the manufacturer. The part of this file that contains confidential data, and which can only be assessed by regulatory authorities, should be sent by the manufacturer directly to the authorities. The non-confidential part of the API master file, is mainly presented in the CEP. Accordingly, the sections of the CTD in which this non-confidential information are filled should refer to CEP.

Regarding the **drug product section** (3.2.P of the CTD), beyond a description of the product and its composition, should also contain information relatively to: the pharmaceutical development; the manufacture; the control of excipients; the control of drug product; the reference standards or materials; container closure system; and stability data (22).

To compile such information, the departments of quality control and pharmaceutical development should provide the data obtained, concerning the studies of their responsibility, to regulatory affairs department.

Data from Bioequivalence studies should be compiled in Module 2 – Quality overall summary of the CTD.

My second day on regulatory affairs department, was spend with Ana Margarida Andrade, responsible for the variations to the terms of a marketing authorisation. She provided me theoretical information about this procedure and the types of variations that may occur. The handling of variations covers the following categories:

- Minor variations of Type IA
- Minor variations of Type IB
- Major variations of Type II

Regulation (EC) N. º 1234/2008 (23) applies to the examination of variations to the terms of marketing authorisations for medicinal products.

The EC "*Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products*" should be consulted in order to properly classify the type of variation.

Concerning **variations of type IA**, such minor variations do not require any prior approval, but the marketing authorisation holder (MAH) must notify, within 12 months following implementation, all Member States concerned or the Agency ("Do and Tell" procedure). Some examples of type IA variations are: deletion of manufacturing sites; or minor change in the manufacturing process of the active substance. However, certain minor variations of type IA require immediate notification (IA_{IN}) after implementation (i.e. change in the name and/or address of the MAH; change in name of the active substance; change in the shape or dimensions of the pharmaceutical form of immediate release tablets, capsules, suppositories) (23).

Variations type IB, must be notified before implementation. The MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ("Tell, Wait and Do" procedure). Some examples of type IB variations could be: change in the name of the medicinal product; minor change to the restricted part of an active substance master file concerning changes in the manufacturing process of the active substance (23).

A **variation type II**, is a "major variation", which means that is a variation that may have a significant impact on the quality, safety or efficacy of a medicinal product. Such major variations require prior approval before implementation ("Prior authorisation" procedure). For this kind of variations a 60- or 90-day evaluation timetable is applied (regarding to the urgency of the matter). Some examples of type II variations are: variations related to the addition of a new therapeutic indication or to the modification of an existing one; variations related to significant modifications of the SmPC due in particular to new pharmacovigilance findings; substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product; changes in the DMF.

For the submission of the variation, there is an appropriate formulary - "*Application for variation to a marketing authorisation*" of the EC – to be filled and sent to the regulatory authorities (23, 24).

The submission of type I variations to INFARMED I.P. can be made through electronic form. Variations of type II should be submitted in paper format.
I had the opportunity to insert some variations in the electronic form in INFARMED´s website, under the supervision of Ana Margarida Andrade.

2.1.6. Business development

Business development involves "the tasks and processes concerning analytical preparation of potential growth opportunities, the support and monitoring of the implementation of growth opportunities"(25).
In Bluepharma, the department of business development (BD) is the company area specifically dedicated to the search of growth opportunities and in establishing strategies to achieve them, in order to increase market competitiveness. These strategies are designed to find business opportunities always at the forefront in relation to competitors. Bluepharma´s BD department was created in 2009 as a result of the identification of a company structural need. BD has been since then vital for the industrial growth, generic drug marketing and to raise direct revenue through the implementation of R&D projects to other companies and technology licensing to third parties. The strategies rely on the strengthening of its portfolio with innovative products and internationalization to new territories, together with the consolidation of its presence in markets already known.
Both in the strategies development or implementation phase, the department collaborates and integrates the knowledge and feedback from other company departments, for example, R&D, production, regulatory affairs, quality assurance, etc., to assure that the organization is capable of implementing the growth opportunity successfully.

During my curricular training I had the opportunity to spend one day in the BD department, in order to get an outline on the relevance of the work performed there for the growth of the company.
André Freitas, head of BD, was responsible for providing me information about the performed activities, which are part of their professional responsibilities.
Firstly, André Freitas addressed aspects about:

- The Bluepharma´s business model (Figure 5);
- The importance and mode of articulation of this sector with other departments;
- The core business of Bluepharma (generate value/knowledge; technology licensing; manufacturing of medicinal products);
- The process from product idea to a final product – product timeline (see Annex 2);
- The use of information repositories (concerning the information about competing products, such as patents, studies, articles, etc.);
- The searching tools for application to the BD in order to find relevant business opportunities (Thomson Reuters: Cortellis e Newport);
- The context of "out-licensing" (to develop Bluepharma´s product and sell it after completion of clinical studies, and before or after marketing authorisation).

Figure 5: Bluepharma´s business model (Source: Bluepharma)

Afterwards, other two topics with special relevance were addressed: CDAs and IP rights.
A CDA is a legal document, which ensures confidentiality of proprietary information that a sponsor gives to another part (i.e. investigator, CRO, client, manufacturer). A signed CDA may be required before any proprietary information transfer, even during the process of request for quotations or negotiation.
The most important information to be taken into account in the CDA content is: the established period for confidentiality preservation; the information covered by confidentiality (clearly stated); District court for decision if an eventual breach of confidentiality occurs (neutral countries would be preferable, such as: England; Switzerland; or Austria).
Concerning the IP protection, André Freitas provided me with an overview about what this is and in the way this influences their work.
IP is a legal concept in which exclusive rights are recognized. IP rights are granted to a variety of intangible assets, such as: musical, literary, and artistic works; discoveries and inventions; and words, phrases, symbols, and designs. Common types of IP include copyright, trademarks, patents, industrial design rights, etc.
André Freitas focused in the types relevant for drug development area: patents (concerning discovery and inventions) and trademark.
Patents are granted anywhere along the development lifeline of a drug (and can include a wide range of claims). Patents expire 20 years from the date of filing, but many other factors can affect the duration of a patent. A patent grants an inventor exclusive rights to make, use, sell, and import an invention for a limited period of time, in exchange for the public disclosure of the invention (a solution to a specific technological problem, which may be a product or a process) (26).
A trademark is a recognizable sign, design or expression, which identifies products or services of a particular source from those of others.

The importance of protection of IP rights (in particular the protection of inventions, industrial design and trademarks) for innovation, employment, competition and thus economic growth, cannot be underestimated.
For generics companies the IP rights of reference products should be respected, and marketing authorisation will only be granted after its patent expiration (20 years).
The theoretical knowledge acquired in BD unveiled to be very useful, particularly in terms of patents and CDA, two extremely important topics for the pharmaceutical area.

2.1.7. Pharmaceutical development

The purpose of pharmaceutical development is to design those aspects related to drug substance (or active substance), excipients, container closure systems, and manufacturing processes that are critical to drug product (or finished product) quality, in order to consistently deliver the intended performance of the pharmaceutical.
Concerning the drug substance, physicochemical and biological properties that can influence the performance of the drug product and its manufacturability should be evaluated (i.e. solubility, water content, particle size, etc.).
Regarding the excipients, their concentration and the characteristics that can influence the drug product performance (i.e., stability, bioavailability) or manufacturability should be evaluated (27).

Aside from its innovative research activities, Bluepharma also conducts extensive activity around the development of pharmaceutical formulations, development and validation of analytical methods, as well as stability and scale-up studies. These activities aim at the development of new generic medicines. The company established several partnership deals with multinational companies upon setting the development of generic medicines for the global market as a goal, with particular emphasis on the European and American markets.

In this department of pharmaceutical development, I learned the general steps of how development of generic medicinal products is performed.
The duration of my internship in this department was 2 days, but these were so intensive, that enabled me to get a general perspective of what is performed here and its importance to the overall activity of the company.
In the first day Sónia Alfar, head of pharmaceutical (galenical & analytical) development, was kind enough to provide me with an overview of the activities carried out in this department as a way of introduction. Her approach only included the steps (in topics, not in detail) for the pharmaceutical development as I present in the table below (Table 6).
In the second day other professionals of this department presented some of these topics in more detail, according to their activities and experience in each area.

Table 6: Steps for pharmaceutical development of generics at Bluepharma

A. Galenical development[6]
A.1. Physicochemical characterization of the reference medicinal product
A.1.1. Mass
A.1.2. Sizes
A.1.3. Impurity profile
A.1.4. Stiffness
A.1.5. Disintegration/dissolution profile
A.1.6. Coating
A.1.7. Content/components
A.2. Formulation development (to develop a formulation similar to the reference product):
1.2.1. Qualitative composition
1.2.2. Quantitative composition
1.2.3. Quality of excipients
1.2.4. Definition of the manufacturing process (i.e. more effective granulation method)
B. Analytical development [7]
B.1. Contents of the formulation (in API and excipients)
B.2. Impurities
B.3. Dissolution profile
B.4. Uniformity of the content/mixture
B.5. Validation of analytical procedure[8]
B.6. Specifications (according to ICH Q6 guideline)
C. Scale-up
C.1. Laboratorial batches (laboratorial scale – i.e. 200 tablets)
C.2. Pilot scale batches[9] (these are generally used in the bioavailability and bioequivalence studies)
C.3. Industrial batches (industrial scale)
D. Stability studies
E. Bioavailability and bioequivalence studies

After this theoretical overview of pharmaceutical development of generics in Bluepharma, Sónia Alfar led me to Rui Saltão, with high experience in stability and bioavailability/bioequivalence (BA/BE) studies, in order to provide me more information about these studies.

Stability studies

Concerning stability studies, Rui Saltão presented me the documents used for the support and appropriate conduct of such studies:

- Guideline ICH Q1A (R2) – Stability testing of new drug substances and products – which provide recommendations on stability testing protocols including

[6] **Galenical formulation** deals with the principles of preparing and compounding medicines in order to optimize their absorption. It is intended by the preparation of drugs using multiple ingredients (27).
[7] The development of analytical procedures is intended to standardise and describe in detail the way of performing each analytical test (32).
[8] The **analytical procedure** refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, use of the formula for the calculation, etc. The objective of **validation of an analytical procedure** is to demonstrate that it is suitable for its intended purpose (32).
[9] **Pilot scale batch** is a batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch (are the minimum units that it is possible to use in the industrial manufacturing equipment). For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger (28).

temperature, humidity and trial duration for climatic zone[10] I and II (EU, US, Japan), and also for III and IV, which is important, since Bluepharma also exports for countries with these range of temperatures and humidity;

- EMA guideline – Guideline on stability testing: Stability testing of existing active substances and related finished products;
- Guideline ICH Q1E – Evaluation for stability data;
- Pharmacopoeias of the API and excipients;
- Information folder of the manufacturer concerning the stability studies conducted in the active substances.

Stability studies should be performed in order to provide evidence on how the quality of the drug substance or drug product varies with time, under the influence of a variety of environmental factors such as temperature, relative humidity (RH), and light; and also to establish a re-test period[11] for the active substance or a shelf-life[12] for the finished product and recommended storage conditions to all future batches manufactured and packaged under similar circumstances.

The approach provided by Rui Saltão was focused only on the conduct of stability studies in the finished product (or drug product), since Bluepharma is not engaged in the manufacture of API´s (this information is provided by the API manufacturer).

Stability studies on drug product should be performed on at least three primary batches of the same formulation and in the package proposed for marketing. Each individual strength and container size should be tested.

Stability studies should include testing of those attributes of the finished product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy.

The stability information should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form. Therefore, considering this available stability information it is possible establishing the acceptance criteria for the shelf life of the drug product.

The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use. There are three types of storage conditions for conducting stability tests: long-term testing; accelerated conditions; and, as appropriate, intermediate conditions (Table 7).

[10] **Climatic zones** - The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions. Zone I temperate (21°C and 45% RH), zone II subtropical with possible high humidity (25°C and 60% RH), zone III hot/dry (30°C and 35% RH) and Zone IV hot/humid (30°C and 65% RH) (28).

[11] **Re-test period** is the period of time during which the active substance, stored under the defined conditions, is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product (28).

[12] **Shelf-life** (or expiration dating period) is the time period during which a drug product, stored under the conditions defined on the container label, is expected to remain within the approved characteristics (28).

Table 7: Types of storage conditions for conducting stability studies (28)

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

Testing under **accelerated conditions** consists in using exaggerated storage conditions in stability studies. They are designed to increase the rate of chemical degradation or physical change of a drug product. These studies can provide information on the behaviour of the drug product when exposed to storage conditions outside of what is recommended, such as those that might occur during shipping. Where significant change occurs at the accelerated condition, then the shelf life would depend on the outcome of stability testing at the intermediate condition, as well as at the long-term condition, as I will describe below (28).

Long-term studies are performed under the recommended storage condition for the time of shelf life proposed for labelling. These studies should be sufficient to establish the stability profile of the finished product. The long term testing should cover a minimum of 12 month´s duration at the time of submission. However, after approval these studies should be continued for a period of time sufficient to cover the proposed shelf life. Extrapolation[13] to extend the shelf life beyond the period covered by long-term data can only be proposed in the marketing application, if no significant changes occur at the accelerated condition (meaning that apparently, the drug product will remain satisfactory within the acceptance criteria for the proposed shelf life). If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and significant change occurs at any time during 6 months, testing at the accelerated storage condition and additional testing at the intermediate storage condition should be conducted (28, 29).

Intermediate testing is conducted at intermediate storage conditions. They are designed to moderately increase the rate of chemical degradation or physical changes for the drug product intended to be stored long term at 25°C. These studies are only performed if a significant change at the accelerated storage condition occurs.

These specific storage conditions, in accordance with these ranges of temperature and humidity, are possible thanks to the climatic chambers.

Photostability testing should also be conducted on at least one primary batch of the drug product (28).

[13] **Extrapolation** is the practice of using a known data set to infer information about future data. In this particular case, it is the use of data from stability testing to infer future behavior of the product in practice. Extrapolation is done as follows, if long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and no change occurs at any time during complete testing at the accelerated storage condition, we can double the number of months of long term studies. However can never be exceeded an addition greater than 12 months. For example, 18 months of long term studies with no changes in accelerate conditions can only add 12 months more, instead of more 18 months (29).

Bioavailability and bioequivalence studies

Concerning BA/BE studies, Rui Saltão made an approach on the importance of such studies and what these are, as I explain next.

In marketing applications for generic medicinal products, the concept of bioequivalence is fundamental. The purpose of establishing bioequivalence is to demonstrate equivalence in quality between the generic medicinal product and a reference medicinal product in order to allow bridging of nonclinical and clinical trials associated with the reference medicinal product. Two medicinal products containing the same active substance are considered bioequivalent, if they are pharmaceutically equivalent (similar in terms of safety and efficacy) and their bioavailability's (rate and extent) after administration, in the same dose, lie within acceptable predefined limits.

Bioequivalence studies are performed in order to demonstrate that the generic drug produced it is between the acceptable limits[14] of biodistribution of the drug within the body when compared to the reference product. In these studies, the plasma concentration time curve (Figure 6) is generally used to assess the rate and extent of absorption. Selected pharmacokinetic parameters and pre-set acceptance limits allow the final decision on bioequivalence of the tested products. The area under the concentration time curve (AUC) reflects the extent of exposure. The maximum plasma concentration (Cmax) or peak exposure, and the time to maximum plasma concentration (tmax), are parameters that are influenced by absorption rate (30).

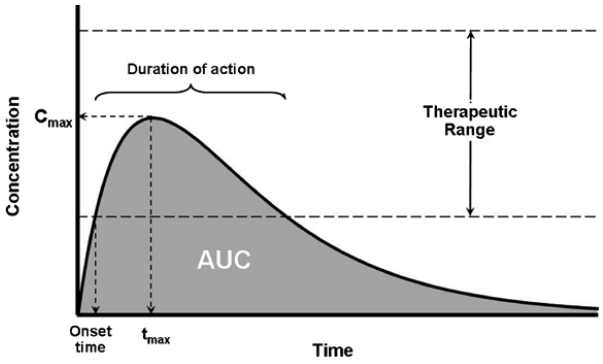

Figure 6: Plasma concentration time curve (31)

The Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products, is the support document for the conduct of such studies (32).

After this theoretical overview provided by Rui Saltão about stability studies and BA/BE studies, I still had the opportunity to contact with other professionals with high experience in other specific activities within this department. These were: Salomé Silva and Ana Pedro from formulation development; and Yara Rocha from method validation

[14] In studies to determine bioequivalence after a single dose, the parameters to be analysed are AUC(0-t), or, when relevant, AUC(0-72h), and Cmax. For these parameters the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of 80-125%. To be inside the **acceptance interval** the lower bound should be ≥ 80.00% when rounded to two decimal places and the upper bound should be ≤ 125.00% when rounded to two decimal places (30).

and implementation. They gave me the opportunity to observe their activities while they were working. With Salomé Silva and Ana Pedro, at the formulation development, I had the opportunity of seeing: powder flow profile (for API and/or excipient) before compression; powder compression to obtain tablets; and granulation method.
With Yara Rocha, I had the opportunity of seeing weighing's of raw materials, the handling of high-performance liquid chromatography equipment and preparation of some admixtures for validation of analytical procedures to be applied in the development of a generic medicinal drug. The validation of the analytical procedure aims at verifying the capacity of this procedure to demonstrate: specificity; linearity; range; accuracy; precision; detection limit and quantitation limit; robustness; system suitability testing. The guideline ICH Q2 (R1) to should be applied for validation of the analytical procedure (33).
Furthermore, I had the opportunity to attend a *Paperclub* about "Quality by Design" (QbD) provided by Rui Saltão, of the pharmaceutical development department, to Bluepharma´s collaborators from all departments.

2.2. Monodisciplinary training

My internship at Bluepharma was mainly for a multidisciplinary theoretic and observational learning. Thus, I consider it a general training that enabled me to perform the specific activities required at TREAT U as an assistant manager.
The role of an assistant manager is to provide all logistical support in order to make the functions of the management team liable of being held. This means to organise the necessary tools and resources for achieving all management requirements.
Assistant managers must be so versatile to the extent of playing a small role in several career areas, such as: administrative, management, accounting, editing, publishing, event planning, marketing, information systems, researcher, graphic or web designer, and other specific functions related with the company´s activity.

My specific training at TREAT U as an assistant manager was held under the supervision and through direct contact with Vera Moura, CEO at TREAT U. The developed activities were focused in three main areas: project management; management of the incentives system; and administrative support.
Prior to joining TREAT U, I have studied in depth its field of research, R&D activities, product pipeline and business model in order to be able to carry out the necessary tasks. For this, Vera Moura was untiring in providing me all the documents and information about the company, which was crucial for my integration into the project achievements and milestones.

2.2.1. Project management

Concerning the R&D activities, TREAT U is currently preparing the scale-up for the product under development.
At the same time, the company is also planning the nonclinical development plan with the preparation of a scientific advice request.
In the following subsections, I will explain my contribution in each of these activities.

2.2.1.1. Scale-up

Pharmaceutical scale-up is the process of product manufacturing from a laboratory scale to production scale (or commercial scale). It is generally defined as the process of increasing the batch size.
In moving from R&D to production scale, it is sometimes essential to have an intermediate batch scale, so-called pilot scale. It is defined as the manufacturing of drug product by a procedure fully representative of and simulating that used for full manufacturing scale. This scale also makes possible the production of enough product for clinical testing and samples for marketing. However, inserting an intermediate step between laboratory and

production scales does not in itself guarantee a smooth transition. A well-defined process may generate a perfect product in both the laboratory and the pilot scale and then fail quality assurance tests in production. Therefore, it is essential to assure that variations in batch size would not adversely alter the quality of the finished product (34, 35).

The manufacturing process development and scale-up will be outsourced. TREAT U is now in the negotiation process with a company, and establishing the CDA and MSA, which I am having the opportunity to follow.
This scale-up process will cover the production of batches for nonclinical and clinical studies, under GLP and GMP conditions, respectively.
For this phase, I have assisted in material acquisition, which involved invoice management and customs deliverance of the ordered raw materials.

2.2.1.2. Scientific advice request

Scientific advice requests are intended for an appropriate design of the studies to support the quality, safety and efficacy of a medicinal product at all stages of the product lifecycle.
Scientific advice helps the company to make sure that is acting in compliance with regulatory requirements, so that no major objections regarding the design of the studies are likely to be raised during evaluation of the MAA. Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of the marketing authorisation. Following the regulators advice increases the probability of a positive outcome (36).
Scientific advice requests are particularly useful to companies developing a medicinal product when: appears to be no or insufficient relevant detail in EU guidelines or guidance documents, or in Pharmacopoeia monographs (including draft documents or monographs released for consultation); or when the company chooses to deviate from the available guidance in its development plan (37).
Scientific advice requests can be submitted to EMA, or to the regulatory authorities of the Member State concerned (i.e. INFARMED, I.P. for Portugal; Medicines and Healthcare Products Regulatory Agency (MHRA) for United Kingdom; etc.). However, scientific advice received from EMA is applicable throughout the EU.
FDA also owns advisory committees (i.e. Oncologic Drugs Advisory Committee) to provide advice on scientific issues, through advisory committees meetings with companies. Recently, EMA and the FDA have initiated a program to provide parallel scientific advice with the goal of exchanging their views and knowledge on scientific issues during the drug development. These parallel scientific advice procedures usually occur at the request of the sponsor, but, in special circumstances, may also be initiated by either EMA or FDA in full cooperation with the sponsor (38, 39).
Concerning EMA, the Committee for Medicinal Products for Human Use (CHMP) gives the scientific advice for human medicines, on the recommendation of the Scientific Advice Working Party (SAWP) (37).

Companies can request scientific advice from the EMA at any stage of development of a medicine, either before submission of a MAA or later on, during the post-authorisation phase. The SAWP/CHMP gives scientific advice by answering questions posed by companies concerning (37):

- Quality (manufacturing, chemical, pharmaceutical and biological testing);
- Non-clinical issues (toxicological and pharmacological tests);
- Clinical issues (clinical pharmacological trials; pre or post-authorisation activities, including pharmacovigilance plans and risk-management programmes); and
- Issues relating to interpretation and implementation of (draft) EU guidelines.

The advice is prospective, it focuses on development strategies rather than pre-evaluation of data to support a MAA, and is given in the light of the current scientific knowledge, based on the documentation provided by the company.
When preparing the scientific advice request it is necessary to ensure that the information and data to be conveyed and discussed with the regulatory bodies are presented in the right way and form. The submission of the requests in conformity with regulators requirements allows it to be evaluated quickly and efficiently by them.
For this reason, these entities make available on their websites support guidances for the request of scientific advice (36, 37).

Therefore, in order to be prepared to give my contribution to this process, I gathered and filed all the necessary information concerning the scope of scientific advices, through EMA´s and INFARMED´s websites.
The EMA provides the "European Medicines Agency Guidance for Companies requesting Scientific Advice and Protocol Assistance", which gives support to companies while preparing and submitting their requests in conformity with SAWP requirements.
The EMA also provides in its website "CHMP protocol assistance scientific advice briefing document template" and a "Template letter of intent for request of scientific advice or protocol assistance" (further explained bellow) (36).
TREAT U is preparing the request for scientific advice for nonclinical development. Thus, my research was focused on the nonclinical issues that may be requested for scientific advice, which are (37):

- Proposals for waiving certain studies or replacing original studies by literature data;
- Deviations or interpretations of CHMP guidelines;
- Specific advice for further evaluation of unexpected findings;
- Study design issues (e.g. species, strain, route of administration, dose groups, groups)
- Pharmacology studies (primary pharmacodynamics concept (*in-vitro* and *in-vivo*) and mode of action, secondary pharmacodynamics, safety pharmacology, pharmacodynamic drug interactions);
- Pharmacokinetics;
- Toxicology studies required (single dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, long-term studies, reproductive and developmental toxicity Inc.

Juvenile studies, local tolerance, immunotoxicity, dependence, metabolites and impurities) (37).

The request for scientific advice should be presented as follows (37):

1. Letter of intent sent by email (to scientificadvice@ema.europa.eu). The deadline for submitting the letter to the Agency Secretariat is approximately 1 month (if no pre-submission meeting is requested), or 2 months (if pre-submission meeting is requested with the letter of intent) before the start of the procedure. It can be sent without any additional documentation attached. The rest of the documents included in the request are to be sent at a later stage (attaching the letter of intent submitted at time of notification).
2. Table of contents of the request.
3. Briefing document including the questions and company's positions. The Briefing document is the most important section of the request. The review by the SAWP will primarily be based on the questions and company's positions presented by the applicant in the Briefing document. It is highly recommended to use the "CHMP protocol assistance scientific advice briefing document template" available in EMA´s website (36), as mentioned above.

Pre-submission meetings that I refer above, which may be requested at the time of submission of the letter of intent, are intended to provide companies the opportunity of:

- Introducing their proposed development programme and receive feedback by EMA staff;
- Receiving feedback on the list of questions to be included in the request for scientific advice, with a view to obtaining satisfactory answers (i.e. content and scope of questions, and structure of the request);
- Identifying additional issues to be included in the request for scientific advice;
- Obtaining more detailed information concerning the procedure for receiving scientific advice/protocol assistance;
- Asking regulatory questions that are outside the scope of scientific advice (e.g. legal basis for submission, GCP/GLP/GMP-related questions, format of MAA or CTD, etc.);
- Establishing contact with the coordinators and EMA staff closely involved with the application as it proceeds.

The discussion during the pre-submission meeting is based on the information provided by the company, in writing and during the meeting. Scientific opinions expressed represent the personal views of the EMA participants and would not necessarily represent the final opinion of the SAWP/CHMP. The pre-submission meeting will allow identification of additional expertise to be involved at an earlier stage in the procedure.

The EMA emphasises the importance of scientific advice or protocol assistance pre-submission meetings with companies, especially for first-time users of these procedures, for SMEs, and for broad and more general advice on specific types of medicinal products.

Scientific advices procedures require the payment of fees. The value ranges for fee are applied in accordance to the type of request (Initial request; or Follow-up to the initial

request), and requested issues (i.e. clinical development; or safety development). The fees applied can be consulted in the EMA guidance for scientific advice requests above mentioned. Orphan medicinal products designated in accordance with Article 5 of Regulation (EC) No 141/2000, are eligible for fee reductions. SMEs are also eligible for fee reductions, fee deferrals and conditional fee exemptions in accordance with Regulation (EC) No 2049/2005 of 15 December 2005.
EMA´s procedures for scientific advice requests are a reference in the EU. Hence, my research has included them. Moreover, this research can be useful for the company future goals (i.e. scientific advice request for clinical trials) (37).

TREAT U is currently preparing the request for scientific advice to submit to INFARMED, I.P., concerning nonclinical development. Thus, to be able to provide support to the company where necessary, regarding the requirements for scientific advice requests to INFARMED, I.P., I gathered the following information on the Regulatory Authority.
INFARMED, I.P., provides regulatory and scientific advice (RSA), through the Regulatory and Scientific Advice Office (GARC), regarding (40):

- Development, manufacture and monitoring of medicinal products (or medical devices) in the areas of quality, pre-clinical and clinical safety, including pharmacovigilance (or vigilance, for medical devices) and risk minimisation, efficacy, economic assessment, licensing, inspection and publicity; and
- Development and manufacture of cosmetic products in the areas of quality, safety, including vigilance and publicity.

Advice can be required during initial development stages and also during post-marketing.
The advice provided by INFARMED, I.P., will only refer to questions to which no clear answer can be found on National regulation or in National or European guidelines (including European and Portuguese Pharmacopoeias). Likewise, INFARMED, I.P., will not provide advice whenever the same advice has been requested to EMA's SAWP (40).
The request for RSA should be submitted in the appropriate GARC form (see Annex 3), available in INFARMED's website (www.infarmed.pt), with the questions to be answered. These questions should clearly identify the main point to be advised on, and provide the adequate framework to the problem. The applicant shall provide its opinion on the subject - "Applicants position" (one page for question in A4 format). Only five questions per area (i.e. clinical, pre-clinical, regulatory, etc.) can be placed in the same request.
These documentation should be sent by e-mail (to garc@infarmed.pt) indicating in the subject: "Request for Advice + Type (medical device/medicinal product/cosmetic product) + Product Name (if applicable)" (40).
After receiving the application and in case of any doubt arising during the assessment, the involved experts can request supplementary information to or plan a meeting with the applicant. The technical and scientific assessment is made by experts in different areas (pharmaceutical, pre-clinical, clinical and BA/BE) from the Scientific Assessment Unit, the Directorate of Medicines Evaluation, and from the Commission of Medicines Evaluation. This evaluation is based on legislation and relevant guidelines applicable, including those published in EudraLex, EMA and ICH (40, 41).

The written opinion is issued by INFARMED, I.P. no later than 90 days. If supplementary information is requested, this time limit shall be suspended until applicant clarification.
If a meeting with a company is convened, it should be scheduled no later than 30 days before the planned closing date. INFARMED, I.P., notifies the company with the issues to be discussed and during the meeting only aspects related to the submitted request shall be approached. Afterwards, within 10 days, the applicant shall send to INFARMED the minutes of the meeting for comments, and these will be finalised by INFARMED, I.P.
Whenever the applicant needs additional information on the issued final opinion, a follow-up request has to be submitted to INFARMED, I.P. with a new set of questions, following the same procedure as the original request.
RSA requests are subject to the payment of fees. Thus, five days after receiving confirmation of the validation of the request (which generally takes 10 days after request submission) the applicant shall pay the appropriate fee. Then, the applicant should send the proof of payment (of the electronic transfer) to the same e-mail (garc@infarmed.pt) along with the completed payment form (40).

2.2.1.3. Nonclinical development plan

Nonclinical safety studies are recommended to support human clinical trials and for the marketing approval of a pharmaceutical. These studies generally include safety pharmacology studies, general toxicity studies, toxicokinetic and nonclinical pharmacokinetic studies, reproduction toxicity studies, genotoxicity studies and, for drugs that are intended for a long duration of use or have special cause for concern, an assessment of carcinogenic potential and other (conducted on a case-by-case basis). (42)
Hence, the goals of the nonclinical safety evaluation are to characterise toxic profile of the pharmaceutical in target organs, dose dependence, relationship to exposure, and in some cases, potential reversibility. Nonclinical information is crucial for the estimation of an initial safe starting dose and dose range for the clinical trials (42).
Animal safety studies should be planned and designed to represent an approach that is scientifically and ethically appropriate for the pharmaceutical under development.
Nonclinical development plan is the compilation of the nonclinical studies needed and the design of each study (i.e., species, number of animals, number of administrations, etc.) according to the type of pharmaceutical under development, to properly characterise the potential toxic effects that might occur in humans during clinical trials (42).
The proper preparation of nonclinical development plan should be based on the requirements provided in:

- ICH guidelines (i.e. M3R2, S6, S9, etc.);
- EMA and FDA guidance's;
- Organisation for Economic co-operation and development (OECD) principles for GLP, which are recognized as the international standard for GLP.

ICH guidelines are applied in the EU, Japan and USA and those are the reference for the development of the nonclinical plan. The guideline basis for nonclinical evaluation is the ICH M3R2 – "Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals" and this will refer to other guidelines (generally safety – (S) – guidelines) to be used according to the specificity of the pharmaceutical.

ICH safety (ICH S) guidelines should be always applied to cover specific aspects of the nonclinical development. ICH has produced a comprehensive set of these guidelines (S1, S2, S3, S4, S5, S6, S7, S8, and S9) to uncover potential risks like carcinogenicity, genotoxicity and reproductive toxicology, and more recently, for assessing the QT interval prolongation liability (ICH S7 B), the most important cause of drug withdrawals in the last years.

For biotechnology-derived products, the types of safety studies conducted in their evaluation should be determined in accordance with the ICH S6 guideline – "Preclinical safety evaluation of biotechnology-derived products" and M3R2 for guidance with regard to timing of nonclinical studies. For pharmaceuticals under development for advanced cancer, guideline ICH S9 – "Nonclinical evaluation for anticancer pharmaceuticals" - should be applied. Other indications in life threatening or serious diseases without current effective therapy might also require a case-by-case approach to both the toxicological evaluation and clinical development to optimise and accelerate drug development.

Already in the course of clinical trials, after the preclinical evaluation, some nonclinical studies will continue to take place (in parallel with clinical studies), providing additional nonclinical safety information as this becomes available (43).

Moreover, both FDA and EMA, provide some guidance's for performing such studies (in accordance to ICH principles) in their websites.

At EMA´s website, Regulatory part, there is a section (called scientific guidelines) where it is possible to consult EMA´s guidelines on the non-clinical testing of medicines (i.e.: for pharmacology, pharmacokinetics, and toxicology studies; general guidelines; and for herbal medicinal products). The Agency's CHMP prepares these scientific guidelines in consultation with regulatory authorities in the EU Member States, to provide a basis for practical harmonisation of how the EU Member States and the Agency interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy that are in the Community directives. The Agency strongly encourages applicants and MAHs to follow these guidelines. Any deviation from guidelines should be fully justified by the applicants at the time of submission. However, it is recommendable to discuss any intention for deviation with EU regulators, during medicine development, through scientific advice (already explained in section 2.2.1.2. of this report) (44).

At FDA´s website, Drugs part, there is a section called "Guidance, Compliance & Regulatory Information" – Guidance's Drugs, where it is possible to consult the "Pharm/Tox" Guidance's intended for the conduct of nonclinical studies (45).

As stated above, nonclinical studies should be conducted in compliance with GLP. The OECD principles for GLP set out the requirements for the appropriate management of nonclinical safety studies. They establish a set of standards intended for: proper planning;

controlled performance of techniques; faithful recording of all observations; appropriate monitoring of activities; and complete archiving of all raw data obtained. GLP Principles also help to define and standardize these processes within research institutions. These standards are not intended to evaluate the scientific value or technical content of the studies, but for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data. These allows ensuring good operational management of each study and keep the focus on those aspects of study execution (planning, monitoring, recording, reporting, archiving) that are of special importance for the reconstruction of the whole study. Moreover, adherence to GLP principles will remove many sources of error and uncertainty, adding to the overall credibility of the study (46).
Only adherence to, and compliance with, all the requirements of the OECD GLP principles constitutes real compliance with GLP (15).
The GLP principles, in their regulatory sense, are only applied to studies that are: non-clinical; designed to obtain data on the properties and/or the safety of items with respect to human health and/or the environment; intended to be submitted to a national registration authority (46).
Independently of the site where the study is performed, GLP principles should be applied. Hence, studies planned and conducted in a manufacturer's laboratory, at a contract or subcontract facility, or in a university or public sector laboratory should be in accordance to these principles. Whatever the industry targeted, GLP stresses the importance of the following main points: resources (organisation, personnel, facilities and equipment); characterization (test items and test systems); rules (protocols, SOPs); results (raw data, final report and archives); and quality assurance (independent monitoring of research processes) (15, 46).

Concerning the activities related to the nonclinical development plan, the knowledge provided by Ana Catarina Pinto at Bluepharma and also the one acquired during the master course, was essential for performing the activities required at TREAT U.
TREAT U is currently preparing the nonclinical development plan for its first product. So, in order to provide support in this process, I acquired a thorough knowledge of the company´s pipeline and gathered the guidelines that should be applied to the product under development.

During my monodisciplinary internship I had the opportunity of participating in scientific meetings between the management team and the company scientific advisors aiming at the development of the nonclinical plan. The participation in these meetings was extremely enriching for developing my knowledge in the regulatory affairs field.
During these meetings, among the many things I learned (which for confidentiality reasons I cannot disclose), I learned where to consult suitable and reliable sources of information. As an example, I learned that the FDA´s website grants access to data of approved drugs (e.g. competitors available in the market), through the Drugs@FDA link, such as: Approval History, Letters, Reviews, and Related Documents.

One of the tasks assigned to me in one of the meetings by Luís Almeida, TREAT U´s scientific advisor, was to search information on related products available in the market, to perform a SWOT analysis, and to gather the information on the nonclinical studies that they have performed and its major findings.
So, in order to accomplish this task, beyond FDA´s website (which I described above), I also consulted: EMA´s website, for Scientific Discussion and EPAR´s; European Pharmacopoeias; SmPC´s and Products Monographs (or product information) provided by the companies; and peer-reviewed articles.
I also had the opportunity of providing support in the preparation of the nonclinical development plan to be proposed for scientific advice.
Since TREAT U is developing a compound for cancer treatment, I have followed the guideline ICH S9 intended for nonclinical evaluation for anticancer pharmaceuticals to identify the type of studies required to support phase I clinical trials (i.e. Pharmacology, initial Pharmacokinetics, General toxicology) and the ones performed in parallel with clinical development to support marketing (i.e. Genotoxicity). Afterwards, I have consulted the corresponding safety guidelines applied for the design of each study; for example, ICH S7A for pharmacology studies design, or ICH S2 for Genotoxicity testing, etc.
Then, in order to simplify the consult of the nonclinical plan, I provided support to Vera Moura in transferring this information from a text format into a table. This allowed crossing the information between each study and: the guidelines applied and its specifications; the scope of the study; the starting time (before or after clinical trials initiation); study design (species, dosage scheme, number of animals); and type of assay/assessment.
I have also prepared a chronogram with the duration and schedule of each nonclinical study to support clinical development and marketing.

I am currently gathering the necessary information to start the preparation of the Target Product Profile (TPP), as recommended by Luís Almeida.
The TPP "is a format for a summary of a drug development program described in terms of labelling concepts" (i.e. Indications and Usage; Contraindications; Adverse reactions; etc.) and it is intended to provide a format for discussions between the sponsor and the FDA (47). Nevertheless, although meetings between TREAT U and FDA are not foreseen for the present moment, organising the TPP will allow to focus the team in the labelling concepts that are intended for the product and to maximize the efficiency of its development program.
So, in order to properly prepare the TPP, I am following the FDA ´s Draft "Guidance for Industry and Review Staff, Target Product Profile – A Strategic Development Process Tool" which provides the purpose of the TPP and a template form.
The TPP can be used throughout the drug development process to support: pre-IND application; IND submission; IND phases (end-of-phase (EOP) 1; EOP 2A (Proof-of-concept); and EOP 2/Pre-phase 3) meetings; Pre-NDA submission; and also in post-marketing programs, to FDA.

The TPP is organised according to the key labelling sections (listed in the guidance) and summarizes the specific drug development studies (both planned and completed) that will supply the evidence for each concept intended for inclusion in the drug labelling. Each section contains the following areas: target[15]; annotations[16]; and comments[17].
TPP is a live document, which means that should be regularly updated as the information becomes available. Thus, the sponsors should complete the appropriate sections (or even add additional subsections) depending on the stage of drug development. Although its submission is not mandatory, it is strongly recommended by FDA (47).

In this phase, where TREAT U is browsing CROs for performing nonclinical studies under GLP conditions, I found useful to start carrying out a SOP to provide support and standardize the process for the identification and selection of a duly qualified service provider to conduct these studies and also for the monitoring of its performance.
In addition to the responsibilities assignment for the tasks, this SOP is intended to include standards for: the preparation of a request for proposal according to study requirements; the process of identification of putative service providers, according to the services intended to be requested; the signature of CDA for information request/exchange; the pre-study qualification site visit; the criteria for the selection (evaluation and comparison of proposals); the study contract signature; the monitoring and/or site audit during the studies; the performance assessment of the service provider following study completion; and for the archiving of study related documentation.
The information provided by Ana Catarina Pinto at Bluepharma was crucial for initiating this SOP and the structure will be very similar to the presented in section 2.1.4. *III.* of this report.
Once this document is completed and approved, it will be implemented in the company.

2.2.2. Management of QREN incentives system

In the attempt to proceed with their R&D activities aimed for the development of nanotechnology-based platforms for drug delivery, TREAT U resorted to the support granted under the QREN incentive systems for "Research & Development companies".
Of the three incentives systems mentioned in section 2.1.2., the SI I&DT is the one applied to the project of TREAT U. The range of I&DT projects [18] is extended to several typologies:

[15] **Target** area should include labelling language, include what sponsors hope to achieve based on the outcome of the indicated studies (47).
[16] **Annotations** area should include summary information regarding completed or planned studies to support the target (47).
[17] **Comments** area should include additional information that can aid understanding - to provide clarity (47).
[18] "I&DT projects" encompasses the R&D activities coordinated and controlled, with a previously defined period of implementation, with a view to carrying out certain objectives and endowed with human, material and financial resources (12)

individual or co-promotion projects for I&DT enterprises; voucher I&DT; collective[19] I&DT; clusters and centres of I&DT; and valuing I&DT (demonstrators projects[20])(12).
TREAT U was granted a financial incentive by the SI I&DT, in co-promotion with the University of Coimbra and NanoDelivery (a spin-off from the University of Minho, Braga). These three co-promotors have celebrated a contract with the Innovation Agency (AdI)[21] in which the project designated as "MultiNanoMed, will benefit from the incentives from QREN in the period between October 2012 and June 2015.
When a project is approved to benefit from the QREN grants, the total value of the incentive is distributed by each group of approved expenses (i.e. Human Resources (HR); raw materials acquisition; services acquisition to third parties; patents; etc.). The total amount of incentive will be assigned in portions throughout the project, upon submission of proof of expenditure. Moreover, the company can only claim reimbursement for approved expenditures (or, eligible expenditures) in accordance with the value that was assigned for that kind of charges.
Throughout the formalisation of the contract between the parties benefiting from the grant, an expenditure execution map is attached and has to be fulfilled, under penalty of contract cancelation during the project.
Thus, the management of the incentives system is a complex process, which involves, dealing with all these conditionings.

When I arrived at TREAT U, the knowledge acquired in the financial department at Bluepharma allowed me to implement and comply with the incentives management system from AdI.
For that, I have started with the compilation of a file with the contract established between AdI and the three co-promotors, e-mails from AdI´s project manager, and other documentation concerning "I&DT projects in co-promotion" (available in the COMPETE website), such as:

- The legislation applicable;
- Guide for filling the application for reimbursement (Management Guidance N. º 04.REV3/2012);
- Payments management guidance updated.

Afterwards, and following the download of the electronic form for reimbursement application, the conditions for the submission of the first request were met.
I was left with the responsibility of submitting the request for reimbursement for both TREAT U (leader promotor) and NanoDelivery (one of the co-promotors).
The management of the first request for reimbursement covered the following steps:

- Selection of the invoices for eligible expenditures;
- Completion of the electronic form for reimbursement request for salaries and invoices, its validation and electronic submission via COMPETE platform;

[19] In this context, **collective** means shared by a significant number of companies (12).
[20] **Demonstrators projects**, aim the divulgation and demonstration of new technologies in the form of new products, processes or innovative services at a national and international level, in order to evidence the economic and technical advantages of the new solutions (12).
[21] AdI is the intermediate body for the analysis, evaluation and monitoring of the SI I&DT projects in co-promotion, included in the program QREN (11).

- Preparation of the documentation (form for reimbursement request printed and signed by the manager and TOC and a copy of the invoices submitted) in paper and in electronic format (e-mail), to send for AdI;
- Interaction with the AdI´s responsible person for the analysis, evaluation and monitoring of the MultiNanoMed project.

There are two reimbursement request types:

- Request for payment in advance (before the settlement of the invoice);
- Request for payment through reimbursement (after the settlement of the invoice).

The company selected the payment scheme in advance. Thus, after the QREN reimbursement, and further settlement of the invoices, I had to submit the supporting evidence of this settlement (i.e. receipts or banking transfers) to AdI.

Other support activities performed were:

- Organisation and archive (in electronic and paper formats) of the invoices and respective proof of payment in the accounting folder, to support the TOC;
- Assure the settlement of the invoices by the Manager.

I voluntarily assumed the responsibility for the overall management of the payment request of the co-promotor NanoDelivery. Therefore, requests for quotation for the laboratory material, contact with National and International suppliers, placing the order and indication of the locals for shipment, receipt of the invoices, management of the sold out products, and insertion of this expenditures in the NanoDelivery´s electronic platform for reimbursement request were the tasks which I had the opportunity to perform.
I also established contact with NanoDelivery´s management team, in order to give them an update on the steps I was following (especially with respect to payments) and to send them the invoices via e-mail, for company accounting reasons.

2.2.3. Administrative support

The experience and knowledge provided by Ana Luísa Santos at Bluepharma concerning administrative tasks, enabled me to develop them independently at TREAT U.
Initially I had the opportunity to count on her support for performing particular tasks at TREAT U, but later on, I was performing them by myself.
Some of these administrative tasks were:

- Preparation of a *Press Release* to TREAT U, in order to promote the enterprise in the media (see Annex 4);
- Preparation of a Briefing for TREAT U for partnerships establishment (Portuguese and English versions) (see Annex 5);
- Minute's meetings preparation;

- Preparation of an e-mail message to introduce TREAT U to potential investors or partners (short message containing the following: enterprise projects; present activities/achievements; and expectations for the future);
- Preparation of a Christmas card and send via webmail to TREAT U´s contacts.

Hereafter, I will describe the activities that I developed independently at TREAT U.

Organisation and Archive

TREAT U is a new enterprise and its office was opened in December 2012. One of my first tasks was organisation and archive of the company´s documents in folders. This archive organisation covered: bibliography relevant for the project (guidelines, guidance's, competitors information, etc.); patent documentation; general documentation; signed CDAs; minutes meeting; invoices; purchase orders; etc.

Annual Report preparation

During these first months at TREAT U, I also had the opportunity to write a draft version of the annual report relative to the company´s activities in the year of 2012 (not the financial chapter). This draft version was then revised by the manager, Vera Moura, and approved for general counsel presentation. Some of the contents of the annual report that I have drafted were: mission and values of the company; framework of activity (which required a strong research on the epidemiology of cancer and sales trends for cancer therapies in the years ahead); nanotechnology applied to oncology area; research activities and recent achievements; financing sources; company networking programmes; IP rights; scientific publications; company presence in the media; efforts for company divulgation; company awards and distinctions; and prospects for the future.

Promotion

Furthermore, as an enterprise that is emerging, TREAT U is currently browsing new potential investors. Therefore, it is fundamental to demonstrate that the company is attractive for investment. In this context the promotion of the company´s activities, achievements, milestones and pipeline, is essential. Within this scope, my contribute was to attend:

- TREAT U´s website management (update of videos and news published in the media; website improvements);
- Briefings for partners and investors (Portuguese and English versions);
- Poster elaboration for results presentation, concerning the project for PEGASEMP™, in the Annual Meeting of the American Association for Cancer Research, April 2013.

Financial Resources

I also supported the preparation of the candidacy for the funds of Portugal Ventures, under the investment programme "Call for Entrepreneurship". The Call for Entrepreneurship is the entry point to the *Ignition Programme*, a new initiative led by

Portugal Ventures to promote investment for market-oriented scientific and technological projects. The *Ignition Programme* focuses on financing projects in the following stages of their life cycle:

- Seed projects (proof of concept to establish that an idea, invention, process or business model is feasible) with a working prototype (even preliminary) that allows to validate the practical application of the technology and/or business idea and with evidence of market value;
- Start-up companies that do not have significant revenue generation (48).

Human Resources

In the context of HR management, I also had the opportunity to collaborate on the selection process of a scholar fellow to attend one of the projects being held by TREAT U in co-promotion with the University of Coimbra and NanoDelivery.

I have received and filed the applications (Curriculum Vitae and motivation letters) electronically. Afterwards, I displayed relevant information about each candidate in a tabular form, according to the selection criteria. This was intended to ease consultation of data and decision making of the jury (professors from the University of Coimbra and TREAT U´s management team). I also wrote the minute concerning the meeting for selection of the candidate.

Meetings

I also provided administrative assistance to Scientific and general Assembly meetings:

- Preparation and distribution of meeting notifications;
- Meeting agenda preparation;
- Minutes of meetings;
- Distribution and archive of minutes;
- Follow-up from the meetings (monitoring of the accomplishment of assigned tasks).

Other tasks performed as an assistant manager:

- Management of the HR according to the company activities and assigned budget (expenditure calculation support for hiring an employee);
- Management of correspondence;
- Quotation requests for services and products (i.e. rent a printer);
- Request for office supplies and equipment (quotation, purchase order, package confirmation and credit memo notes);
- Receptionist functions (handling incoming and outgoing mail, e-mail and phone calls);
- Management and maintenance of electronic archives and records;
- Requests for quotations for raw materials and laboratory material, from both National and International suppliers.

3. Discussion

In this topic I will present a brief description of my 6-months "on-the-job" training experience as an assistant manager.
This description includes the areas I was involved in, a consideration on the achievement of training objectives, encountered difficulties and challenges, a personal opinion about my experience on a pharmaceutical industry versus a spin-off company, and also the large applicability of the knowledge acquired in the master's course to the developed activities.

Areas of involvement
In my multidisciplinary training I had the opportunity of passing through diverse departments of Bluepharma (administrative, financial and accounting, quality assurance, regulatory affairs, business development, R&D, and pharmaceutical development). This experience allowed me to have a perspective on the importance of the departments individually and also in articulation with each other, for the company dynamics and for the achievement of its overall goals.
The experience at each department, allowed me to acquire multidisciplinary skills and competences that contributed to the activities performed in my monodisciplinary experience at TREAT U as an assistant manager.
The assistant manager has to provide support to the management team in various and sometimes, dissimilar activity areas. Therefore, at TREAT U, I had to perform several activities that are inherent to the function (administrative support and management of the incentives system) and also some non-inherent activities, more related with my academic background, such as project management activities: assistance in the preparation of the scientific advice request, as well as starting the preparation of the TPP; and help in the preparation of the nonclinical development plan, which are activities that meet the current needs of the company.

Encountered difficulties and Challenges
During my specific training, the major difficulty I encountered was the lack of experience as an assistant manager (particularly for administrative activities and of management of an incentive system). This represented a challenge, but, at the same time a great motivation to achieve the required knowledge in order to perform adequately all inherent activities.
The theoretical knowledge acquired in the administrative and financial departments at Bluepharma helped me to overcome the majority of these difficulties. Others, I have handled on my own based on personal experience and through adequate research. The combination of these experiences was crucial for performing the activities for which I had no academic background, and were of extreme importance for meeting the company's goals and needs at this early stage.
Furthermore, the knowledge acquired in the regulatory affairs department at Bluepharma did not cover the activities I would have to accomplish at TREAT U, since these companies work with different pipelines. Thus, the required skills had to be fully developed at TREAT

U, namely in what concerns the preparation of the scientific advice request, which demanded an extensive research of adequate information.
The same happened in the experience at the quality assurance department. The knowledge acquired there was more applied to the development and manufacture of generic medicines, which did not fit in TREAT U's activities. However, this was an excellent contribution to understand the dynamics of the pharmaceutical quality system and the overall standards of a certified company.

Accomplishment of goals
The main goals established for my curricular training were to be able to practice autonomously and efficiently assistant manager functions and to apply the theoretical knowledge acquired in the master's course to the real work world.
In my opinion these goals were completely achieved, since I was able to accomplish the assigned tasks independently at TREAT U, taking advantage of the knowledge and skills acquired in the master's course and also developed within an R&D innovative enterprise. Beyond this, the participation in internal scientific meetings was extremely enriching for developing my knowledge in regulatory affairs. Therefore, I may say that these main goals were fully achieved.
Other specific goals achieved throughout the training were the acquisition and/or development of soft skills, such as:

- Communication skills (tact and diplomacy; writing of correspondence and administrative documents);
- Interpersonal relationships (teamwork, working contacts network establishment);
- Organizational skills;
- Professionalism sense and integrity;
- Discretion and respect for confidentiality and compliance for policies and procedures;
- Capacity for dealing with emerging difficulties, exercise of creativity and the development of critical attitude;
- Problem solving, initiative sense and decision making;
- Deadlines accomplishment and to work under pressure.

Other developed hard skills were:

- Capacity for the writing of English technical documents; and
- Informatics (website management, outlook tool).

In the light of this, I was able to notice my personal, social and professional growth provided by the accomplishment of the tasks and through the interpersonal relationships within two distinct companies.
Thus, I may say that at the end of my curricular training, my initial objectives have been achieved and this has been a very rewarding experience.

Pharmaceutical Industry versus Academic Spin-off experience

Throughout my curricular training I had the opportunity to experiment two different realities: one from a proficient pharmaceutical company and another from an academic spin-off enterprise.

The reality provided by the training at Bluepharma (through regulatory affairs, quality assurance, business development and pharmaceutical development departments) was focused mainly on the manufacturing and marketing of generic medicinal products, since Bluepharma´s R&D activities are performed in partnership with other enterprises. Nevertheless, to learn more about the R&D activities in my multidisciplinary training, Bluepharma gave me opportunity to be in contact with one of its partner companies – the spin-off Luzitin, to get a perspective on the nonclinical development.

At TREAT U, a spin-off enterprise, I had the opportunity of having contact with the beginning of the development of a product that emerged from findings of a research group of the University of Coimbra, with the intent of its commercialisation. At this early stage of product development, I had the opportunity of following product optimisation and preparation of the nonclinical development plan.

I can say that fortunately I had the opportunity of having two different perspectives within the pharmaceutical sector: from a generics industry and from a company of innovative medicines, which was a very enriching experience; and, although the dissimilarity of these two different realities with the background knowledge acquired through the master's course I can say that I have felt comfortable and familiar with the concepts I was learning.

Application and development of the knowledge acquired in the master's course

I would like to point out that the skills and knowledge acquired during the Pharmaceutical Medicine master's course were crucial for the performance of the activities and tasks required during my curricular training experience. Particularly I would like to emphasize, the contribution of some of the curricular units, for example:

- "Medical writing and communication" for preparing a poster for presentation of the project of TREAT U at the Annual meeting 2013 of American Association for Cancer Research;
- "Clinical development" for the preparation of a SOP for the selection and monitoring of a service provider for nonclinical studies;
- "From drug discovery to first-in-human" for the support in the preparation of the nonclinical development plan.

I also would like to highlight the contribution of the exercises performed in the curricular units throughout the course, with large applicability in the real working environment, which provided great support to the developed activities.

4. Conclusion

The master's course provides a curricular plan in accordance to the main activity areas of the pharmaceutical sector. The knowledge acquired in all curricular units allows each student to understand the different areas which, when combined, provide an overall view of the pharmaceutical development.
Thus, even hereafter working at a specific area, this general perspective on the different areas of the pharmaceutical sector enables us to know what each department does and how they impact the overall company's activities.

The "on-the-job" training curricular unit aims at developing the knowledge and skills acquired throughout the master´s course by applying them on a day-to-day basis in the real world, and also finding an area with which the student identifies better.
My curricular training as an assistant manager enabled me to deepen my knowledge in regulatory affairs (such as preparing a scientific advice request) and in nonclinical development planning. Moreover, the opportunity to participate in the scientific meetings held by the company was a very important milestone for my skills development.

The success of this training experience was mainly due to the people with whom I had the opportunity to work. At Bluepharma, each department that I visit welcomed me very well. The professionalism of its collaborators and willingness to teach contributed for my easy adaptation and integration within the company.
At TREAT U, the management team also very well welcomed me. I was treated and recognized as a member of the working team, and assigned with responsibilities and duties equivalent to an independent employee.

Finally, say that the writing of this report allowed me to consolidate the acquired knowledge and realise the dimension of the contribution of this 6-month multidisciplinary experience to my personal and professional growth.

The continuous improvement of my skills and knowledge throughout my career is a goal I intend to follow firmly in order to be prepared for every challenging experience and work opportunities.

I would like to say that having attended this master´s course, with which I identified myself from the beginning, allowed me to grow personal and professionally, and has also given me the opportunity to work in an area I have always been interested in.

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Annex 1

Travel Plan for a Bluepharma employee

Dia 1: 13-12-2012 – Quinta

Saída de Combra: Estação Coimbra-B às7h47
Chegada a Lisboa: Estação Oriente às 9h22
Apanhar o Metro: Oriente – Alameda – Roma/Areeiro
(O INFARMED fica na Av. Do Brasil, a 500 metros da Estação de metro Roma-Areeiro)

Inicio do Programa de formação (INFARMED): 10 Horas

Estadia no Hotel Lutécia
Av. Frei Miguel Contreiras, N.52, 1749-086 Lisboa
Contatos:
(A Estação de Metro Roma-Areeiro fica a cerca de 200 metros)
Check-in ao final do dia (deixar mala no hotel, que fica a 200m do metro, ou no INFARMED)

- Confirmação em anexo

Dia 2: 14-12-2012 – Sexta

Estadia no Hotel Lutécia

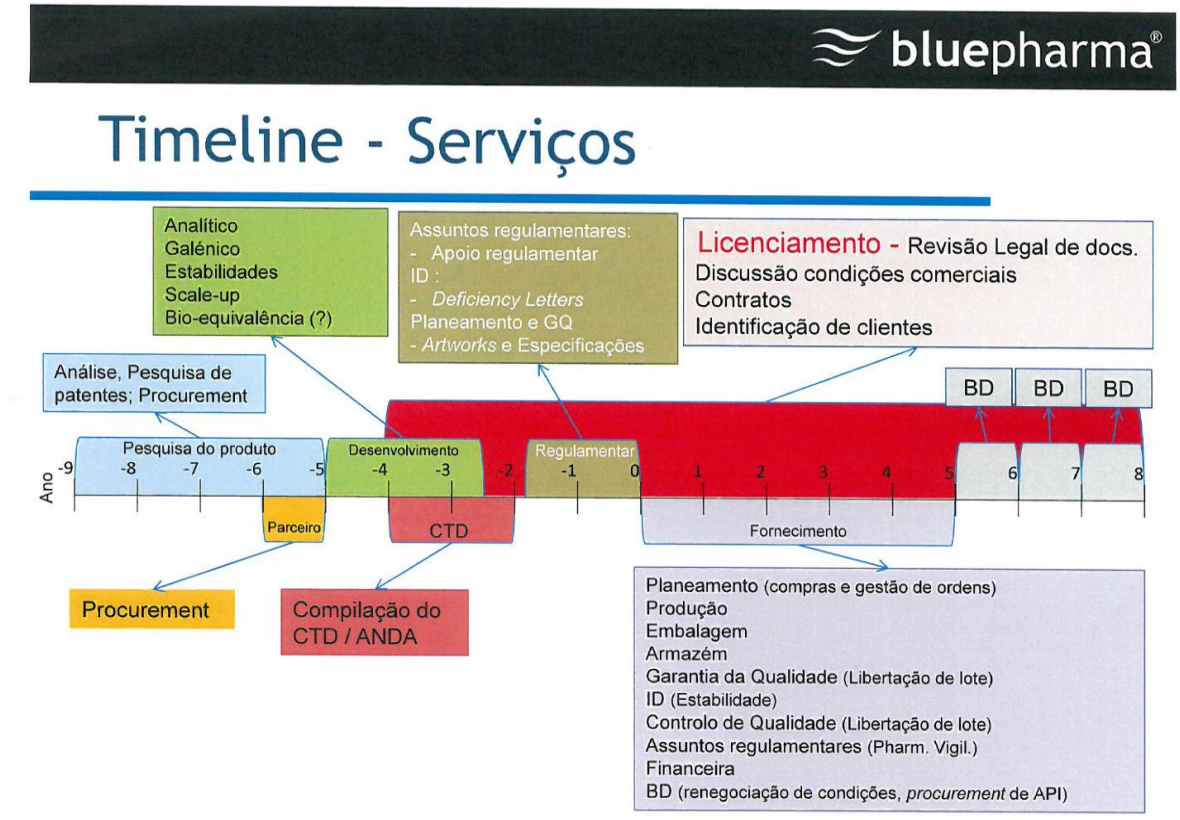
Dia 3: 15-12-2012 – Sábado

Apanhar o Metro: Roma/Areeiro – Alameda – Oriente

Saída de Lisboa (AP): Estação Oriente às 18h09
Chegada a Coimbra: Estação Coimbra-B às 19h47

Annex 2

Bluepharma BD - The process from product idea to a final product – product timeline


bluepharma®
Timeline - Serviços
Analítico
Galénico
Estabilidades
Scale-up
Bio-equivalência (?)
Assuntos regulamentares:
- Apoio regulamentar
ID :
- Deficiency Letters
Planeamento e GQ
- Artworks e Especificações
Licenciamento - Revisão Legal de docs.
Discussão condições comerciais
Contratos
Identificação de clientes
Análise, Pesquisa de patentes; Procurement
BD
BD
BD
Pesquisa do produto
Desenvolvimento
Regulamentar
Ano
-9
-8
-7
-6
-5
-4
-3
-2
-1
0
1
2
3
4
5
6
7
8
Parceiro
CTD
Fornecimento
Procurement
Compilação do CTD / ANDA
Planeamento (compras e gestão de ordens)
Produção
Embalagem
Armazém
Garantia da Qualidade (Libertação de lote)
ID (Estabilidade)
Controlo de Qualidade (Libertação de lote)
Assuntos regulamentares (Pharm. Vigil.)
Financeira
BD (renegociação de condições, procurement de API)

Annex 3

GARC Form, for Request of Regulatory and Scientific Advice to INFARMED I.P.

REQUEST FOR REGULATORY AND SCIENTIFIC ADVICE

MEDICINAL PRODUCTS FOR HUMAN USE

Form to be sent to: garc@infarmed.pt

Characterisation of the Request for Regulatory and Scientific Advice (Fill in when relevant)	
1. ☐ First request of Advice Number of request: _____ ☐ Follow up request Number of the first request: _____	**Date:** **(Mandatory field)** **Date:**
2. Agencies where the request has been or will be submitted **(Mandatory field; one or more options)**	☐AT ☐BE ☐CY ☐CZ ☐DE ☐DK ☐EE ☐EL ☐ES ☐FI ☐FR ☐HU ☐IE ☐IS ☐IT ☐LI ☐LT ☐LU ☐LV ☐MT ☐NL ☐NO ☐PL ☐SE ☐SI ☐SK ☐UK ☐EMA ☐None
3. Applicant's identification **(Mandatory field)**	**Name:** **Address:** **Telephone:** **TeleFax:** **Email :** **Contact person:**
4. Legal representative of the applicant **(Mandatory field)**	**Name:** **Address:** **Telephone:** **TeleFax:** **Email :** **Contact person:**
5. Type of advice **(Mandatory field; one or more options)**	☐ Regulatory ☐ Scientific

6. Scope of the Scientific Advice **(Mandatory field; one or more options)**	☐ Pharmaceutical ☐ Pre-clinical ☐ Clinical ☐ Pharmacokinetics ☐ Classification issues/ Borderlines: ☐ Medicinal Products/ Medical Devices ☐ Medicinal Products/Other Health Products ☐ Good Practices. Please specify which: ☐ Pharmacoeconomic studies ☐ Risk Management Plan and Pharmacovigilance ☐ Authorization of entities ☐ Publishing of advertising ☐ Other Please specify which: _____
7. Aim of the Advice **(Mandatory field)**	☐ R & D ☐ Marketing Authorization Request ☐ Type IA Variation nº _____ ☐ Type IB Variation nº_____ ☐ Type II Variation ☐ Variation with equivalent value to a Marketing Authorization ☐ Renewals ☐ Reimbursement request ☐ Other. Please specify which: _____
8. Date for submission of the request (previewed)	
9. Stage of development of the medicinal product	☐ Pre-clinical ☐ Phase I clinical trials ☐ Phase II clinical trials ☐ Phase III clinical trials ☐ Approved
10. Authorisation status of the medicinal product in other EU Member States A – Authorised P – Pending R – Revoked S – Suspended N – No Marketing Authorisation request **(One or more options)**	☐AT ☐BE ☐CY ☐CZ ☐DE ☐DK ☐EE ☐EL ☐ES ☐FI ☐FR ☐HU ☐IE ☐IS ☐IT ☐LI ☐LT ☐LU ☐LV ☐MT ☐NL ☐NO ☐PL ☐SE ☐SI ☐SK ☐UK

11. Type of prodedure	☐ Centralised procedure ☐ Mutual Recognition ☐ Decentralised procedure ☐ National procedure ☐ To be defined
12. Legal Basis for the Marketing Authorization request, or legal basis under which it was authorized, according to Directive 2001/83/EC (current version)	☐ Article 8(3) application (i.e. Request with administrative, quality, pre-clinical and clinical data) ☐ Article 10(1) generic application Reference medicinal product in Portugal: _____ ☐ Article 10(3) Hybrid application Reference medicinal product in Portugal: _____ ☐ Article 10(4) Similar biologic application ☐ Article 10a well-established use application ☐ Article 10b fixed combination application ☐ Article 16a Traditional use registration for herbal medicinal product
13. Documents in annex **(Mandatory field)**	

Details about the medicinal product /Health product (Fill in when relevant)	
14. Name of the medicinal product /health product	
15. Active substance	
16 Strength	
17. Pharmaceutical form	
18. Route of administration	
19. Therapeutic indications	
20. Pharmacotherapeutic group (ATC-Code)	
21. Brief description of the mechanism of action	

Additional comments:

It is hereby declare that the information provided above is correct and true and it was not submitted to the Scientific Advice Working Party of the European Medicines Agency.

Signature: _____ Date: ___/_____/_____

Question for Regulatory and Scientific Advice
Question:
Applicant's position:

Annex 4

TREAT U - *Press Release*

Tecnologia inovadora para o cancro da mama

Nanopartícula que previne o aparecimento de efeitos secundários da quimioterapia

A TREAT U é uma *spin-off* da Universidade de Coimbra, fundada em Janeiro de 2010, com sede em Coimbra.
A TREAT U encontra-se ligada ao Centro de Neurociências e Biologia Celular da Universidade de Coimbra, ao Biocant, bem como à Bluepharma – Indústria Farmacêutica, S.A..
Os seus sócios-fundadores Vera Moura, João Nuno Moreira e Sérgio Simões possuem uma vasta experiência nas áreas de biotecnologia e tecnologia farmacêutica tendo obtido os seus graus de Doutoramento em Universidades e Centros de Investigação de excelência.

Esta empresa tem como missão produzir tecnologias inovadoras e competitivas para o tratamento do cancro, de forma a proporcionar ao doente oncológico terapêuticas mais seguras e mais eficazes no tratamento da doença. Isto traduz-se em benefícios, não só para o próprio doente, mas também para as entidades prestadoras de cuidados de saúde, pela esperada diminuição da necessidade de intervenções cirúrgicas e de internamentos.

Com foco nas limitações das terapêuticas convencionais, nomeadamente na baixa seletividade para o tumor, a TREAT U dedica-se ao desenvolvimento de nanopartículas que permitem encapsular um fármaco (ou combinações de fármacos) com atividade terapêutica, transportá-lo ao longo da corrente sanguínea e entregá-lo especificamente no seu alvo – o tumor.
Estas nanopartículas permitem obter uma elevada concentração de fármaco apenas no tumor, não causando os efeitos secundários decorrentes da acumulação nas células sãs dos outros órgãos.

A TREAT U encontra-se atualmente envolvida em dois projetos de Investigação e Desenvolvimento, aprovados no âmbito do Sistema de Incentivos à Investigação e Desenvolvimento Tecnológico do QREN, tendo

sido angariado um incentivo financeiro no valor de cerca de um milhão de euros.

A primeira nanopartícula em desenvolvimento pela TREAT U, denominada PEGASEMP™, foi, patenteada nos EUA em Julho de 2012 e encontra-se em avaliação na Europa. PEGASEMP™ distingue-se das outras plataformas já existentes pela capacidade de atuar não só nas células cancerígenas mas também nas células endoteliais dos vasos sanguíneos do tumor. Em laboratório, os primeiros estudos realizados em animais com cancro da mama humano demonstraram que a plataforma PEGASEMP™ consegue percorrer todo o organismo até atingir o tumor sem provocar toxicidade nos restantes órgãos, suprimindo a invasão das células cancerígenas.

Neste momento, a TREAT U prepara-se para iniciar os primeiros testes de segurança e toxicidade em animais, de acordo com as *guidelines* em vigor, e espera-se que em 2015 se iniciem os primeiros estudos em doentes com cancro, a fim de demonstrar a sua eficácia.

Annex 5

TREAT U´s Briefing for partnerships establishment (English version)