Universidade de Aveiro
2012

Secção Autónoma de Ciências da Saúde

RAQUEL ALEXANDRA PIRES PINELA

9 MONTHS EXPERIENCE AS A TRAINEE REGULATORY AFFAIRS OFFICER

ESTÁGIO DE 9 MESES COMO GESTORA DE ASSUNTOS REGULAMENTARES

RAQUEL ALEXANDRA PIRES PINELA

9 MONTHS EXPERIENCE AS A TRAINEE REGULATORY AFFAIRS OFFICER

ESTÁGIO DE 9 MESES COMO GESTORA DE ASSUNTOS REGULAMENTARES

Relatório de estágio à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Doutor Ricardo Andrade, Coordenador do Departamento de Manutenção no Mercado da Phagecon – Serviços e Consultoria Farmacêutica, Lda., e do Doutor Bruno Gago, Professor Auxiliar Convidado da Universidade de Aveiro.

the jurors

president	Doctor José Carlos Fontes das Neves Lopes Auxiliary Professor, University of Aveiro
principal arguer	Doctor Alexandra Isabel Cardador de Queirós Coordinator Professor without Aggregation, University of Aveiro
supervisor	Doctor Bruno Miguel Alves Fernandes do Gago Invited Assistant Professor, University of Aveiro

acknowledgments

I would like to publically express my thankfulness towards some persons who, directly and indirectly, made this internship possible and contributed for the elaboration of the present document, namely:

Professor Luís Almeida and Professor Bruno Gago, for the amazing effort and enthusiasm during the 2 years of Pharmaceutical Biomedicine master.

To Phagecon's team, for the excellent learning opportunity.

To family and close friends, for unconditional support.

palavras-chave

Medicamento, Medicamento veterinário, Autorização de introdução no mercado (AIM), Titular autorização de introdução no mercado (TAIM), Assuntos regulamentares, Renovação da AIM, Alteração da AIM, INFARMED, I.P., Direcção-Geral de Veterinária (DGV)

resumo

O presente relatório tem como objetivo descrever as atividades desenvolvidas no âmbito do estágio curricular na área dos assuntos regulamentares, que decorreu entre 1 de Agosto de 2011 e 4 de Maio de 2012, no Departamento de Manutenção do Mercado da Phagecon – Serviços e Consultoria Farmacêutica, Lda.. Este estágio é parte integrante do programa de formação do mestrado em Biomedicina Farmacêutica e teve como principais objetivos a aquisição de experiência na realização das atividades comumente associadas aos assuntos regulamentares, bem como a consolidação de conhecimentos e o desenvolvimento de novas competências técnicas.

O primeiro capítulo introduz o estágio curricular em assuntos regulamentares, seguindo-se uma descrição generalista do contexto regulamentar aplicável às atividades realizadas. Os capítulos e secções posteriores destinam-se a descrever a empresa que proporcionou o estágio, os objetivos para este definidos e as atividades e tarefas desempenhadas. Por último, será feita uma discussão crítica do estágio, incluído a análise das principais dificuldades sentidas e as competências adquiridas.

keywords

Medicine, Veterinary medicinal product (VMP), Marketing authorization (MA), Marketing authorisation holder (MAH), Marketing authorization renewal, Marketing authorization variation, Regulatory affairs (RA), INFARMED, I.P., Direcção-Geral de Veterinária (DGV)

abstract

This report aims to describe the activities performed during the curricular internship in regulatory affairs, which took place from August 1, 2011 to May 4, 2012 at Marketing Maintenance Department of Phagecon – Serviços e Consultoria Farmacêutica, Lda.. The internship is an essential part of the training programme in Pharmaceutical Biomedicine and it main goals were: to gain experience in conducting common regulatory activities; to consolidate background knowledge and to develop new technical skills.

The first chapter introduces the internship and is followed by a general description of the regulatory environment applicable to the activities performed. The later chapters and respective sections intend to: describe the hosting company, define internship goals and give a detailed description of the activities and tasks performed during this 9 months experience. Finally, it will be presented a critical discussion of internship outcomes, including the analysis of the main difficulties and key competences acquired.

Index

List of Figures

List of Tables

List of Abbreviations

AD – Administrative Department

ADR – Adverse Drug Reaction

CHMP – Committee for Medicinal Products for Human Use

CP – Centralized Procedure

CRO – Contract Research Organization

CTD – Common Technical Document

DAM – Direcção de Avaliação de Medicamentos

DAM-UMM – Direcção de Avaliação de Medicamentos – Unidade de Manutenção no Mercado

DCP – Decentralized Procedure

DGRM – Direcção de Gestão do Risco de Medicamentos

DGV – Direcção-Geral de Veterinária

EC – European Commission

EDQM – European Directorate for the Quality of Medicines & HeathCare

EMA – European Medicines Agency

ESVAC – European Surveillance of Veterinary Antimicrobial Consumption

EU – European Union

FDA – Food and Drug Administration

GAVM – Grupo de Avaliação dos Medicamentos Veterinários

GMP – Good Manufacturing Practices

INFARMED, I.P. – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

ICH – International Conference on Harmonization

MA – Marketing Authorisation

MAH – Marketing Authorisation Holder

MedDRA – Medical Dictionary for Regulatory Activities

MMD – Marketing Maintenance Department

MRP – Mutual Recognition Procedure

NCA – National Competent Authority

ORIMED – Online Regulatory Information on Medicines

PF – Process Form

PL – Package Leaflet

PMS – Project Manager Software

PRAC – Pharmacovigilance Risk Assessment Committee

PSUR – Periodic Safety Update Report

QMS – Quality Management System

QRD – Quality Review Documents

RA – Regulatory Affairs

RD – Register Documents

R&D – Research and Development

SmPC – Summary of Product Characteristics

USA – United States of America

VMP – Veterinary Medicinal Product

WP – Written Procedure

WI – Work Instruction

INTRODUCTION

The Training Programme in Pharmaceutical Biomedicine offers its students the opportunity to make a curricular internship during the second curricular year. I decided to make the curricular internship in the field of regulatory affairs (RA), because I wanted to put into practice and to test all the competences developed during Biomedical Sciences degree and the first year of this master.

The internship as a RA officer took place in Coimbra, at Phagecon – Serviços e Consultoria Farmacêutica, Lda., more specifically at Marketing Maintenance Department (MMD), responsible for all the projects related to the post-marketing phase of medicines, cosmetics, medical devices and biocide products. It was predicted to start at September 1, 2011 and finish at May 31, 2012 (9 month duration). However, due to outsourcing processes, paternity leaves and holidays, it was suggested to start 1 month earlier. Thus, the internship began at August 1, 2011 and finished at May 4, 2012. During the complete internship period I respected the regular working period, (9 AM to 6 PM) under the supervision of Ricardo Andrade, MMD's coordinator.

The first chapter of this report is dedicated to the hosting company characterization, including foundation history, internal organization and general working methods. After that it is possible to find a comprehensive description of all the activities and tasks assigned and concluded during the 9 months internship. This description is organized in 2 main sections: transdisciplinary experience and monodisciplinary experience. For each activity or project type it will be presented: a legal and regulatory introduction, the general procedures that are usually undertaken and, finally, my personal experience, the knowledge acquired and main difficulties felted.

The last chapter is dedicated to the discussion of the entire experience and to the over whole balance of the 9 months internship experience.

State of Art

Medicines are an essential tool in the field of healthcare and hold particular importance for society, since they have contributing to the improvement of several health indicators during the latest decades, such as the increase of life expectancy and quality of life, or even the decrease of morbidity. Through the development, manufacturing and marketing of medicines, pharmaceutical industry also contributes largely for local economies growth and development (1, 2).

Despite the undeniable benefits of medicines, they can also present several risks which can lead to persistent disabilities or even death, like it happened with thalidomide in the 1960s. Unfortunately, due to this drastic events associated to medicines exposure it was mandatory to develop pharmaceutical legislation in order to implement control mechanisms intended to minimize and mitigate medicines' risks (3). In this context, pharmaceutical legislation major goals are the protection of public health by promoting measures that enhance medicines' safety, quality and efficacy. To accomplish this objective, pharmaceutical legislation it continuously under change in order to respond to new challenges or problems previously not identified. New legislation can also be developed to simplify the current legal status making it more clear and easy to understand, or even as part of the process of adaption to science's advances (4).

For several decades, each country developed its own laws and regulations, which differ largely from country to country, leading to a very heterogenic and complex legislative framework. These differences turned out into global trading difficulties, at the same time pharmaceutical industry became more international and sought worldwide expansion. The obligation to respect different requirements leads very often to tasks duplication and consequently to unnecessary time and money consumption (5).

In this context, it was urgent to standardize procedures and requirements. This was first initiated in 1980s by the European Community, as an attempt to establish unique requirements across the member states, allowing creating a unique and internal market for pharmaceuticals. This same objective is maintained in the current perspective of European Union (EU), which efforts on harmonization are not just focused on medicines, but also on biocides or cosmetic products.

It was also established a central authority, European Medicines Agency (EMA), which coordinates the scientific resources available for evaluation and supervision of medical products, giving advice and support national competent authorities (NCA). In Portugal, INFARMED, I.P. is the responsible entity for manage all national activities related to human medicines, medical devices and cosmetic products. On the other hand, Direcção-Geral de Veterinária (DGV) is responsible for veterinary medicinal products (VMP).

Later on, during 1990, the positive results of European effort for harmonization contributed to the establishment of a new entity dedicated to work on international harmonization on pharmaceuticals requirements for registration, the International Conference on Harmonization (ICH). ICH is constituted by members of industry and regulatory authorities from Europe, United States of America and Japan, who work together on the development of guidelines and recommendations, which will then be implemented on each region. Other entities with interest on ICH activities had been invited to participate as observers (5).

The greatest achievements of ICH, such as the harmonization of Marketing Authorization (MA) request contents (presented below), are the result of scientific consensus between industry and regulatory entities and the commitment to implement and to respect the final guidance (5).

The ultimate result of legislation harmonization procedures is the currently highly regulated environment for medicines, since their early phase of development up to post-marketing phase, embracing the entire medicines' lifecycle.

Medicines' Lifecycle

The development of new and innovate medicines represents the ultimate goal of research and development (R&D) activities developed by pharmaceutical industry. R&D projects for the development of innovative medicines are extremely long (10 to 15 years), expensive (between 800 million dollars and a 1 billion dollars), complex and risky (1). Thus, R&D of medicines presents several challenges for pharmaceutical industry, which ends up contributing to the extremely high level of competitiveness among different companies.

The R&D of a new medicine first takes place with the search for molecules that may have a positive pharmacologic effect in the human body. After optimization of these molecules, the R&D process moves on to non-clinical studies, in order to obtain safety, pharmacologic and pharmacokinetic information. The evaluation of the collected information regarding its implication on human subjects will determine whether or not human trials should be performed. Thus, if non-clinical results reveal potential positive results in humans, the molecule will advance in R&D process to clinical studies. Each clinical study will be specifically designed to answer a well-defined and relevant question and should respect all the applicable legislation and requirements. Clinical trials can be classified accordingly to the time they occur during clinical developed or by their objectives. Clinical trials are typically divided in 4 phases:

- Phase I – usually performed in a small number of healthy volunteers, these studies intend to better define the medicine's safety profile in humans. The most common type of studies is human pharmacology studies, which objectives may include to: assess tolerance, describe pharmacokinetics and drug metabolism.
- Phase II – developed with a relatively small number of patients, usually without further complications associated. Therapeutic exploratory studies are the most commonly performed during this phase, their principal objectives are to: describe the relationship between dose and physiological answer and estimate the optimal doses that should be used in next studies, as well as endpoints and methodologies.
- Phase III – involves large groups of patients, so that it is possible to confirm medicine's efficacy and to better define its safety profile. It is essential that these therapeutic confirmatory studies provide all the needed information to determine a positive benefit-risk balance, essential to obtain MA approval.
- Phase IV – it takes place after MA is granted and it intends to evaluate the therapeutic use of medicine in common clinical practice, which is a far less controlled environment than clinical trials. Through phase IV studies it will be possible to: complete medicine's safety and efficacy profiles or identify rare adverse drug reactions (ADR) (1, 6).

Nevertheless it is important to take in consideration that this temporal division of clinical trials does not defines the order in which studies are performed, since certain kind of studies may be developed in several phases, as depicted from figure 1 (6).

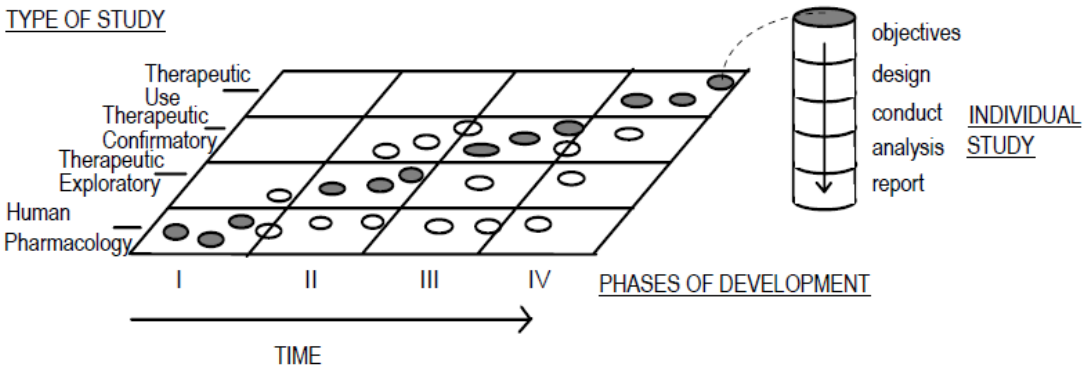


Figure 1 – Relationship between clinical development phases and type of studies, reproduced *from reference (6)*

As mentioned at the end of phase III, the pharmaceutical company developing the medicine expects to have collected all necessary information on safety and efficacy to prove medicine's positive risk-benefit relationship.

However, before any new medicine can be introduced on the European market it has to have a valid MA, granted by a competent authority. At this point it is crucial to define the regulatory strategy for MA request preparation and submission. There are different procedures to request a MA, namely:

- Centralized Procedure (CP). MA request is submitted to EMA and evaluated by experts' committees. If granted the MA will be valid in all EU member states.
- Decentralized Procedure (DCP). The applicant will submit the MA request simultaneously in several EU member states, to the respective NCAs. One of the member states will be appointed as the reference member state and will be responsible by the detailed analysis of the request and the elaboration of the report. This report will then be evaluated by the other NCA. This procedure is possible only if there is no MA in any of the EU member states.

- Mutual Recognition Procedure (MRP). The process is similar to DCP, however there is an initial MA request to a single member state NCA. After MA is granted it is requested to other member states NCAs to recognize the MA on their own countries.
- National Procedure. This process is used when the applicant intends to request a MA valid in a single country. The authority responsible for the evaluation will be the NCA of the concern member state.

Independently from the procedure chosen, MA request is submitted together with the MA dossier, which has a well-defined structure and organization, commonly noun as Common Technical Document (CTD). CTD is one of the many harmonization products of ICH and it became mandatory for new MA requests submitted to Europe and Japan competent authorities, being strongly recommended by USA competent authority (Food and Drug Administration – FDA). Figure 2 shows CTD structure and organization (7).

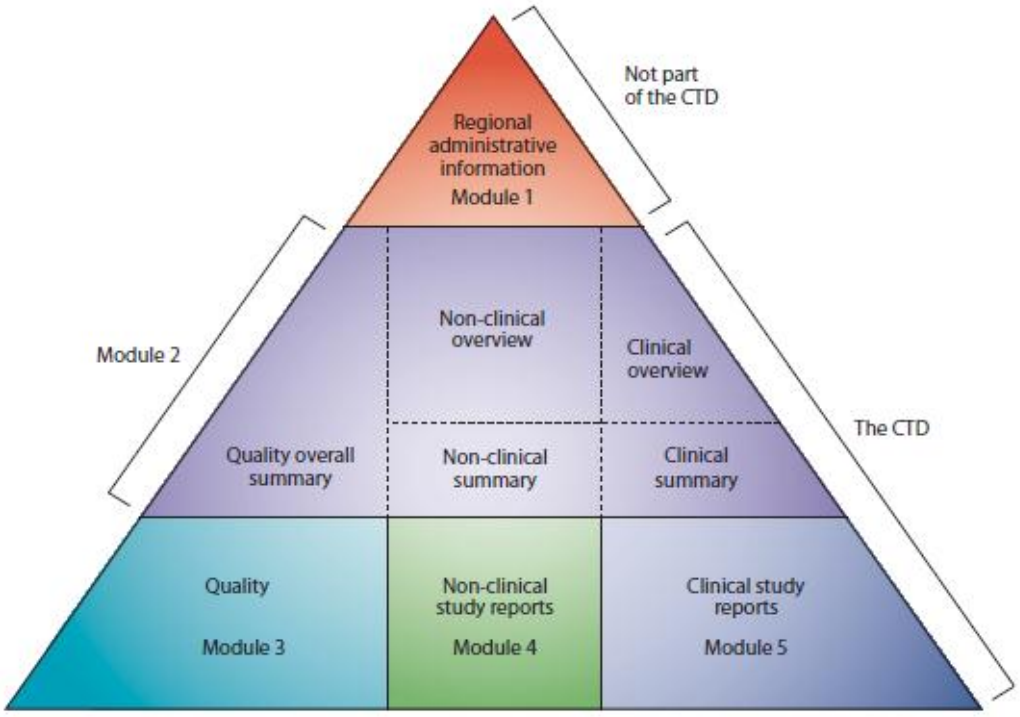


Figure 2 – Common Technical Document Organization, reproduced *from reference (7)*

Despite the fact that Module 1 is specific for each region, including the specific MA request form or proposed product information texts. The other 4 modules should

be common to the 3 regions. This brings great advantage for pharmaceutical industry, since it allows preparing a single dossier regarding medicine's safety, efficacy and quality for different world regions, which ultimately saves time, resources and money (7).

Additionally, documents and information included on each CTD´s modules should respect the dispositions of the latest versions of ICH guidelines regarding this subject, namely:

- M4 (R3): Organisation of the common technical document for the registration of pharmaceuticals for human use.
- M4Q (R1): The common technical document for the registration of pharmaceuticals for human use: quality.
- M4S (R2): The common technical document for the registration of pharmaceuticals for human use: safety.
- M4E (R1): The common technical document for the registration of pharmaceuticals for human use: efficacy.

At European level, and as trend of harmonization within EU, some documents presented on CTD should also follow defined templates. It is the case of product information texts, which includes Summary of Product Characteristics (SmPC), Package Leaflet (PL) and labelling. Product information templates and contents are defined by the Working Group on Quality Review of Documents (QRD), an experts group of EMA (8). QRD latest versions are available at EMA's website in word format and in all EU languages, so that they can be easily used.

The terms used on product information texts should be in accordance with Medical Dictionary for Regulatory Activities (MedDRA) and with the list of standard terms defined by the European Directorate for the Quality of Medicines & HealthCare (EDQM) (8).

Although obtaining MA for a new medicine is an unquestionable measure of success after years of work and effort, it does not mean that all activities concerning that medicine are finished. In fact, it is quite the opposite, since in this new phase of medicine's lifecycle new information can come up at any time and it

will be necessary to maintain MA dossier updated, through regulatory procedures defined in legislation, noun as MA variations. In practical terms, MA variations represent changes to the initially approved information, thus they should be submitted to the competent authorities.

If the Marketing Authorisation Holder (MAH) has the intention to maintain the medicine on the market, the MA needs to be renewed. In this circumstance, a MA renewal request should be submitted to competent authorities, so that they can ensure that the benefit-risk balance remains positive.

Regulatory Affairs

RA professionals play important roles at each step of products' lifecycle, from their early development phase through post-marketing activities. They will be the responsible for ensuring compliance to the applicable regulatory framework, which demands for an extensive technical knowledge and expertise, under continuous development and updating.

RA professionals have multidisciplinary knowledge and their areas of expertise embrace science, law and business. They can work in different entities, namely pharmaceutical industry, government agencies, competent authorities and contract research organization (CRO) (4).

From industry and CRO perspectives, RA professionals may be responsible for:

- Collect and organize all the information and documents required for medicines' MA request or biocides, cosmetic products or medical devices registration processes.
- Identify the need of medicines' MA variations, prepare and submit those accordingly to the applicable legislations.
- Give technical support to company's regulatory strategy definition.
- Make a regular review of new legislation, both under preparation and already implemented.

The efficient performance of these activities is essential to decrease competent authorities' evaluation timing, contributing to save human and financial resources, and to faster provide quality products to general population. Simultaneously it is possible to avoid sanctions for non-compliance with applicable regulations.

The absolute respect for legislation dispositions will ultimately contribute to the recognition of the company's high quality standards, not just by general public and regulatory authorities, but also by competitors and potential clients, in CRO's perspective.

Internship Goals

At the time my internship at Phagecon began, I had no practical experience on RA activities, despite having the basic science and regulatory knowledge.

In this context, the following goals, to be achieved until the end of my internship, were established:

- Develop depth knowledge on RA and medicines legal framework.
- Become familiarized with the real standards and procedures of RA most common activities, which should be respected in order to obtain regulatory approvals.
- Be able to think analytically and critically analyse new legislation and its potential impact on current regulatory practice.
- Strengthen personal skills such as organization and communication.
- Be capable of handle several tasks and projects simultaneously and prioritize them.
- Efficiently manage deadlines.
- Contribute to Phagecon's internal objectives and success.

In short, the internship goals can be resumed to the acquisition of professional experience within the field of RA and the development of new skills that can bring competitive advantages in the job market.

Host Company Presentation

Phagecon – Serviços e Consultoria Farmacêutica, Lda. is a portuguese CRO, founded in January 2006, which is dedicated to provide quality services to pharmaceutical industry within the scope of regulatory, medical and scientific affairs and pharmacovigilance.

Phagecon is part of a large "group" of companies, including:

- FHC Farmacêutica, Lda.. Founded in 1998 with objectives focused on exportation of pharmaceutical products. Currently it remains dedicated to the international management distribution and logistics, operating in several countries of Europe, Africa, Middle-East and Latin America (9).
- Empipharma. Located in Coimbra and was also founded in 1998, it is dedicated to storage and distribution of pharmaceutical products within Portugal. Empipharma core business is the wholesale and pre-wholesale activity in Portugal (9).
- Overpharma – Produtos Médicos e Farmacêuticos, Lda.. Was founded in 2001, with location in Lisbon, and it is dedicated to hospital market wholesaler in Portugal. Currently presents a large portfolio of disposable materials, medical devices and some medicines (9).
- Laboratórios Basi – Indústria Farmacêutica, S.A.. Acquired in 2007 to establish a brand in pharmaceutical market, both national and international. Basi is dedicated to the manufacturing, galenic development and licensing of several medicines with different pharmaceutical forms (9).
- Zeone – Informática, Lda.. Founded in 2008, it offers technic consulting services in IT field, such as software development, web design or informatics assistance (9). In this context it also gives informatics support to all companies of the "group".
- Paracélsia. The takeover took place in 2011; it is dedicated to the manufacturing of large volume parenteral solutions (9).

At the foundation date, the main Phagecon's clients were the companies from the "group". As a result of Phagecon's establishment in the CRO portuguese market, currently there is a large percentage of external clients.

Phagecon presents a wide range of services to its national and international clients. The services' portfolio is constantly being adapted to better respond to the ever-changing market requests and demands. As a result, new services can always be developed and added to those presented on table 1.

Table 1 - List of Phagecon's services organized by specialization area, *adapted from reference (10)*

Specialization Area	Scope of Action
Regulatory Affairs	Medicines Medical Devices Cosmetics and Personal Hygiene Products Food Supplements Biocides
Pharmaceutical Affairs	Quality Management Systems Good Manufacturing Practices Good Laboratorial Practices Auditing Safety, Hygiene and Health at Work
Scientific Affairs	Expert Reports Advertisement and Promotional Materials Technical Translations
Pharmacovigilance	Local Representation Pharmacovigilance Pharmacovigilance Systems (development and implementation) Periodic Scientific Literature Screening

	Periodic Safety Update Reports Typed II Safety Variations Risk Management Systems (development and implementation) Surveillance of Medical Devices and Cosmetics

In August 2011, Phagecon had a 12 full-time employees team, distributed for several departments accordingly to their area of expertise, and experts contacted occasionally within specific projects to perform periodic tasks. The organogram shown in figure 3 identifies the several departments and their hierarchic relationship.

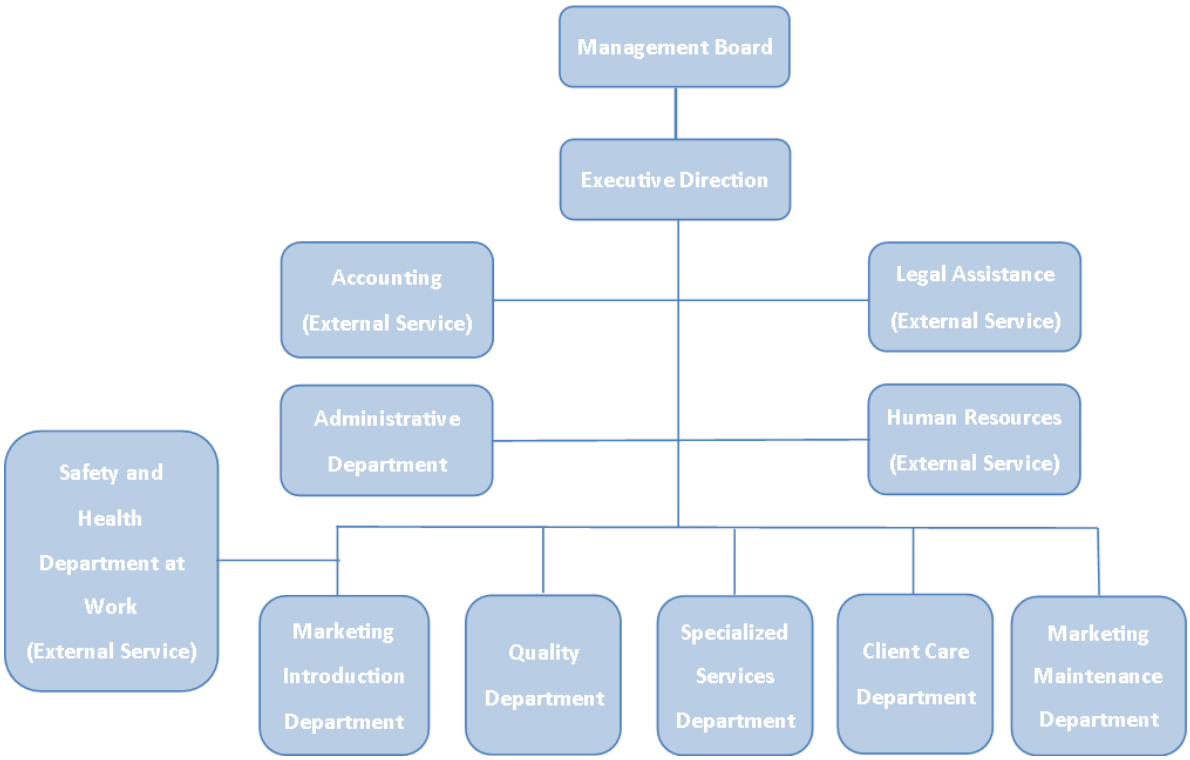


Figure 3 – Phagecon's Organogram, *adapted from reference (10)*

During 2010 Phagecon gained the certification for its Quality Management System (QMS), from the multinational Bureau Veritas. Through this process Phagecon assumed an internal and external commitment of high level and quality in all

process developed at the company. A certificated management system brings great benefits since it enhances efficacy of all tasks developed, at the same time it promotes the recognition and trust of current and future clients.

QMS is described in detail at QMS manual, which is a core document to understand QMS principles and their implications on the performance of daily tasks. In this context, I was given training on this topic, which contents will be described on the further sections of this report.

ON-THE-JOB TRAINING IN REGULATORY AFFAIRS

The present chapter of this report intends to describe in detail all the activities and tasks developed during the curricular internship at Phagecon. It is organized in 2 main sections: the transdisciplinary experience and the monodisciplinary experience.

The first will describe the coaching events which learning outcomes were essential to the performance of several projects tasks, accordingly to Phagecon's established processes. In this perspective, these learning outcomes were present in all the activities performed, in other words, they are relevant to the complete internship.

On the other hand, the monodisciplinary experience section describes the specific activities or tasks performed during the major part of the internship, presenting a detailed description to each one.

Transdisciplinary Experience

This section is intended to describe the learning outcomes of all coaching events which I had the opportunity to participate during the internship. Their learning outcomes were put into practice during the performance of several activities and tasks assigned during the internship and were essential to achieve success.

The training events I attended to during this internship were subordinated to the following themes: general presentation of Phagecon's QMS; operational principals of project manager software and basic pharmacovigilance concepts. A detailed outline of each theme is given below.

Phagecon's Quality Management System

Besides the deep knowledge of the several experts working at Phagecon, the quality of services provided to clients is also ensured by a certificated QMS.

QMS is described in detail at QMS manual, which is a living document suffering changes whenever considered important to fit company's necessities and goals.

I was first introduced to QMS at time internship began and refresh sessions were done every time a new version was launched and as a preparation to the *Bureau Veritas* annual audit.

Currently QMS is on the 4th Edition, dated March 3, 2012 and it is a central document that identifies Phagecon's daily tasks and their interactions, disclosures responsibilities and clearly states the company's goals for the future, i.e. company's vision - "being a company with financial stability and globally recognized by its competence" (10).

QMS manual also establishes Phagecon's mission, i.e. the roadmap for achieving the defined goals, as following: "contribute for the pharmaceutical sector success, especially regarding pharmaceutical industry and distribution activities, through the presentation of services of their interest, which are innovative, personalized and executed by a group of specialized collaborators who guarantee the quality of the services" (10).

Everyday Phagecon's team works to achieve the established goals, trough the execution of several tasks, each one of these belonging to one of the following nine processes (group of activities) (10):

1. Define strategy.
2. Resources supply.
3. Market analysis.
4. Services development.
5. Answer to possible clients contact.
6. Plan the project.
7. Support project's execution.
8. Project execution.
9. Evaluate and improve outputs.

These nine processes are applicable to the different departments and they do not take place exactly on this order, since they can interact with each other as presented on figure 4.

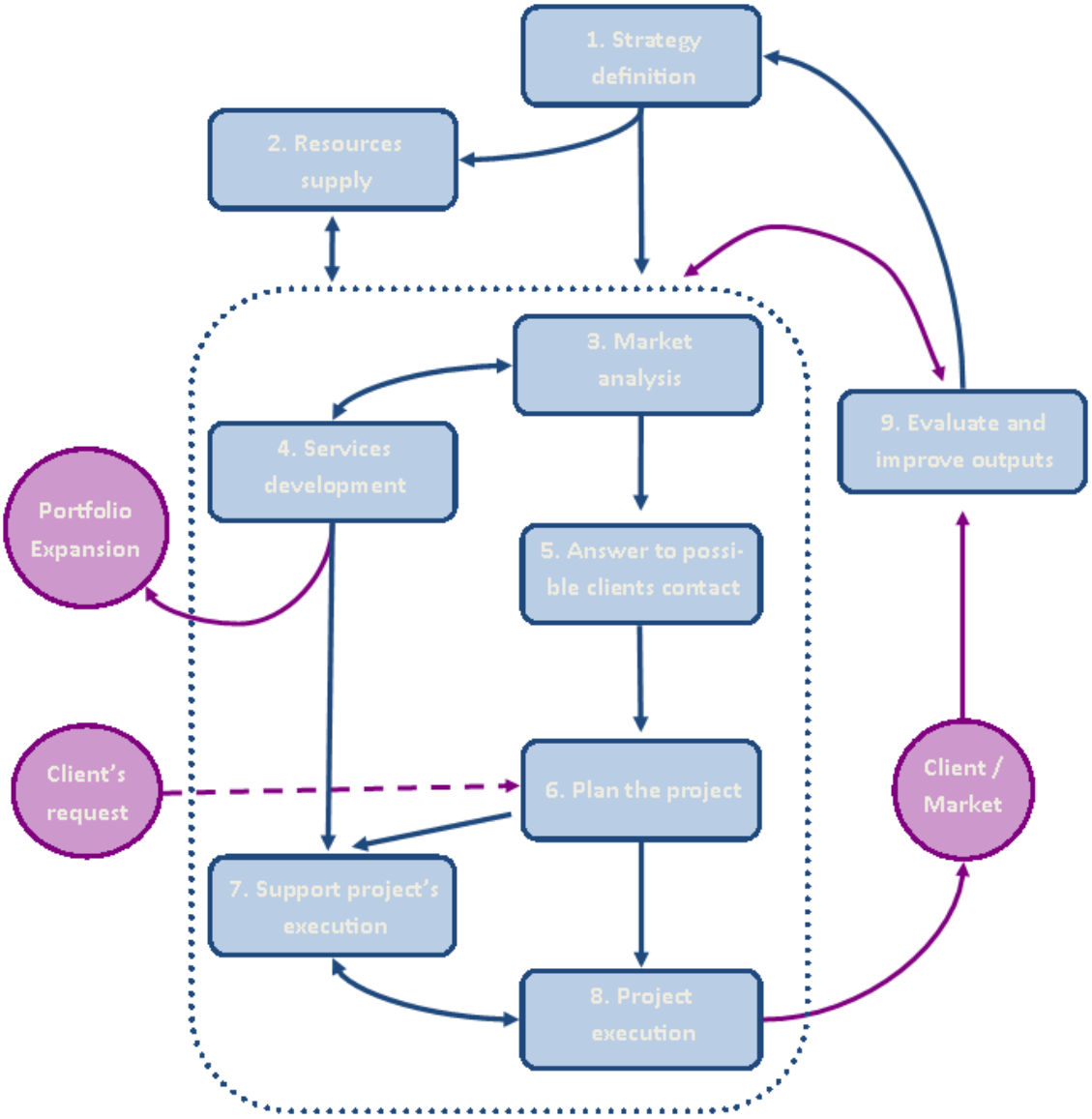


Figure 4 – Relationship of Phagecon´s quality defined processes, *adapted from reference (10)*

The processes within the delimitation line correspond to the activities that take place frequently in order to complete the services offered. On the other hand, the processes placed outside the delimitation line are dedicated to the evaluation and support of QMS.

Identifying and studying the processes occurring at Phagecon and their interactions allow defining the best strategy to deliver the main outcome: high quality services personalized to each client needs. As a consequence of new strategies implementation, QMS will be under continuous improvement and company's efficacy will be sequentially higher (10).

A highly organized and effective QMS requires control over the documents generated within its scope, in other words it requires a structured documental management system. In Phagecon's QMS different document types are organized hierarchically, from the most general to the most detailed as following (10):

1. QMS manual.
2. Processes Forms (PFs).
3. Written Procedures (WPs).
4. Work Instructions (WIs).
5. Register Documents (RDs).

Each one of the 9 processes previously identified has its own PF, which globally describes the activities taken and identifies the responsible collaborator.

For the purpose of this internship, the activities I developed belonged mostly to the processes number 7 (project plan) and 9 (project execution). In this context, PF number 7 and 9 were important documents for me to get familiarized with the general tasks that should be performed for each project and their correct sequence.

On the other hand, both WPs and WIs describe activities executed at Phagecon, present the sequence of operations to be performed for specific projects and activities (10). The lecture of these documents previously to the initiation of certain project types was useful, since they gave me a comprehensive description of all steps to be performed.

Finally the RDs result from the execution and implementation of QMS and include registration forms, plans, general templates, lists, among others.

Project Manager Software - Online Tool

An important tool that helps the execution of some QMS processes, such as planning or executing, is the online Project Manager Software (PMS).

PMS is accessed through the restricted area of Phagecon's website and it displays all the closed out and on-going projects.

Each project has a cover page with a simply description and the identification of the client, the Phagecon´s responsible manager and the project charged value.

There is another project specific page, dedicated to planning and execution, where the responsible manager is able to define the tasks that should be performed, its deadlines and responsible persons for execution and revision. After project plan is complete, it is submitted for department coordinator revision. At this point project manager software will block the project and no more tasks can be introduced or even updated, until the project is approved. In my particular situation MMD's coordinator was the responsible collaborator to create my new projects on project manager software and to approve my planning for each one of those.

After project approval, and as it progresses, each task shall be updated with the amount of time spent every day until its conclusion, as well as any relevant information (whenever applicable).

Since I was responsible for several projects, the initial coaching on the functionalities of this online tool was essential for me to complete all the fields properly, including the initial planning and daily updates.

As a result of these functionalities, online PMS enables project manager or department's coordinators to close monitoring the projects in real time, enhancing productivity and efficacy.

On the other hand, online PMS also gives top management the opportunity to evaluate the productivity of each employee by the analyses of daily reports containing all the tasks introduced in the different projects, in a certain day. Initially I was asked to print the daily report and archive it in the proper dossier, to be evaluated by the executive director. However, technological innovations applied to the initial PMS lead daily reports to be directly sent to executive director's e-mail, at the end of each working day.

Pharmacovigilance – Basic Concepts

As previously indicated, Phagecon offers pharmacovigilance services to several clients. In this context, everyone working at Phagecon must have basic pharmacovigilance knowledge in case it is necessary to record an ADR spontaneous notification.

This basic knowledge was transmitted to me in simple training event, followed by a quick quiz. Most of the topics discussed were in accordance with the knowledge acquired during the biomedical science degree and pharmaceutical biomedicine master, including:

- Pharmacovigilance history.
- ADR definition.
- Pharmacovigilance importance and goals.
- Difference between ADR and adverse event.
- ADR spontaneous notification advantages and disadvantages.

The last point discussed constituted new information to me, since it was related to the essential information to be collected during an ADR spontaneous notification. Thus in case I received any type of communication (phone call, e-mail, letter or personal) regarding an ADR of a client's product, I should collect, at least, the following information:

- Name and contact of the person who is notifying.
- Description of the suspected ADR.
- Medicine suspected of causing the ADR.
- Patient identification.

During the 9 months internship I never had to put in practice the knowledge reviewed and acquired during this training event.

Monodisciplinary Experience

As the title indicates this section is dedicated to the individual activities on which I participated during the internship. Each type of activity took place at a defined moment, but it was usually repeated several times, within the scope of similar project types.

Activities' description is organized by product type. Thus, there will be 2 main subsections: the first is related to human medicines and the second to VMPs.

Human Medicines

The latest legislation defines medicinal product as:

"Any substance or combination of substances presented as having properties for treating or preventing disease in human beings;

or

Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis" (11).

This subsection gives details on the human medicine related activities performed during the internship, including: MA variations, transfers and renewals and also multilingual notifications for labelling and package leaflets.

Marketing Authorisation Variations

During medicines' life cycle MAH may need to adjust or amend the information submitted at the time of MA request, in order to: update productions methods to current technologies; undertake changes demanded by competent authorities, like

INFARMED, I.P.; or even to bring up to date manufacturers chain, among many others possibilities.

MA variations can be classified as major or minor accordingly to its:

- Impact on the already approved information.
- Potential risk to public health.
- Possible impact on medicine's quality, safety and efficacy.

Similarly to other RA activities, MA variations are highly regulated by european and national legislations. From August 2011 to April 2012 the legislation applicable to MA granted by centralized, decentralized or mutual recognition processes should follow the disposition of *Regulation (EC) No 1234/2008 of 24 November 2008*. On the contrary, nationally authorized products (MA conceded by INFARMED, I.P., valid for portuguese territory only), should respect the national law, particularly the *Decreto-Lei n.º 176/2006, de 30 de Agosto* (12).

For future reference, it is important to take in consideration that a new European Regulation concerning MA variations was recently published. Regulation (EC) No 712/2012 of 3 August 2012 introduces several changes to the previous regulation, including the extension of its scope to MA variations of medicines nationally authorized. In Portugal, the application of the new regulation to nationally approved medicines will came into force from August 4, 2013 (13).

Hereupon, and considering that all MA variations projects I undertake during the internship were related to nationally authorized medicines, all the procedures described are referent to the applicable legislation at that time (*Decreto-Lei n.º 176/2006, de 30 de Agosto*).

Accordingly to portuguese applicable legislation, MA variations can be classified as:

- Type IA.
- Type IB.
- Type II.
- Transfer of MA.

Further details on each one of these MA variations, including the regulatory procedures to be respected, the major learning and also difficulties felts while developing this kind of projects, are presented on the following pages.

Type I Variations

Overall Requirements

Type I variations correspond to those with the lowest risk regarding medicines' safety, efficacy or quality. The accepted type I variations are listed at the guidance note "Guideline on dossier requirements for Type IA and IB notifications" (14). This guidance also encompasses, for each variation, the conditions that must be satisfied as well as the list of documentation to be submitted, including the relevant parts of MA dossier that should be updated. For each variation, the guidance also specifies the variation type in IA or IB and assigns an identification number (14). All the information is displayed in a simple manner by the use of tables, as depicted from the excerpt presented on figure 5.

9	**Deletion of any manufacturing site (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place)**	**Conditions to be fulfilled**	**Documenta-tion to be supplied**	**Procedure type**
		None	**1**	**IA**
	Conditions: None			
	Documentation			
	1. The variation application form should clearly outline the "present" and "proposed" manufacturers as listed in section 2.5 of the (Part IA) application form.			

Figure 5 – Example from European guidance regarding type I variations classification and requirements, *reproduced from reference (14)*

Despite the fact that different type I variations may have specific and unique documentation to be submitted, as identified in the referred guidance note, there is a board-spectrum set of documentation which is generally requested independently the variation to be submitted. In this context, for each MA variation project I was involved in I had to prepare the following set of documents (15):

- MA dossier sections modified as consequence of variation.
- Proof of payment of applicable fees and the corresponding guide of payment duly completed.
- Identification of other MA variations already presented or to be presented in a near future, related to the same MA.
- Reviewed SmPC, PL and labelling versions (whenever the variation implies changes in product information texts).

Generally type I variations are intentionally undertaken by MAH, concerning company's regulatory, manufacturing or marketing strategies. However, there is a particular type I variation that is a consequence of referral procedures, which on its turn result from an EC Decision, becoming mandatory in all EU countries (16, 17).

Referral procedures may be invoked by the EC, any member state or any company that markets the medicine in matter, under well-established circumstances, which conducts to different referral types. INFARMED, I.P.'s nationally authorized generic products are most commonly affected by 2 types of referrals (16, 18):

- Divergent decision referral – when it is identified a need of harmonization of national competent authorities' decisions concerning the authorization, suspension or withdrawn of a certain medicine, as established by article 30 of directive 2001/83/EC. There are examples of harmonization needs across European Union the authorization of different indications or posology for the same medicine or similar medicines (reference and generics).
- Community interest referral – if public health protection measures are considered necessary, as a consequence of newly identified concerns related to the quality, safety or efficacy of a certain medicine or class of medicines, as established by article 31 of directive 2001/83/EC.

After the initiation of the referral procedure, the question under study will be analysed by EMA's specialized committees, usually Committee for Human Medicinal Products (CHMP) or Pharmacovigilance Risk Assessment Committee (PRAC), if the issue is related to medicines' safety. The final recommendations for

a certain medicine or class of medicines follow an established format, which includes:

- Opinion page, which presents the referral scope and legal basis.
- Annex I, listing of all medical products affected by the referral, organized by member state and including for each medical product the invented name, MAH and approved strengths, pharmaceutical forms and route of administration. An example of EC recommendation annex I can be analysed in figure 6.
- Annex II, which presents the reasons and conclusions leading to the recommendation made.
- Annex III, that represents the english harmonized proposal for SmPC, PL and labelling that will have to be implemented by all MAH which medicines are affected by referral procedure (18). An example of EC recommendation annex III can be analysed in figure 7.

Member State EU/EEA	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
PT - Portugal	Labesfal - Laboratórios Almiro, S.A. Zona Industrial do Lagedo 3465-157 Santiago de Besteiros Portugal	Nimesulida Labesfal	100 mg	Tablet	Oral use
PT - Portugal	Labesfal - Laboratórios Almiro, S.A. Zona Industrial do Lagedo 3465-157 Santiago de Besteiros Portugal	Nimesulida Labesfal	100 mg	Granules for oral suspension	Oral use
PT - Portugal	Laboratori Guidotti, S.p.A. Via Livornese, 897 I-56010 La Vettola – Pisa Italy	Nimesulene	100 mg	Granules for oral suspension	Oral use
PT - Portugal	Laboratórios Basi - Indústria Farmacêutica, S.A. Rua do Padrão, 98 3000-312 Coimbra Portugal	Nimesulida Basi	100 mg	Tablet	Oral use
PT - Portugal	Laboratórios Basi - Indústria Farmacêutica, S.A. Rua do Padrão, 98 3000-312 Coimbra Portugal	Nimesulida Basi	100 mg	Granules for oral suspension	Oral use
PT - Portugal	Laboratórios Inibsa, S.A. Zona Industrial da Abrunheira –	Nimesulida Inibsa	100 mg	Tablet	Oral use

Figure 6 – Example of EC Recommendation Annex I, *adapted from reference (19)*

Amendments to be included in the relevant sections of the Summary of Product Characteristics and Package Leaflet for nimesulide containing medicinal products for systemic use, as relevant

The following wording is deleted (~~strikethrough text~~), added or moved (underlined text) within the same section of the SmPC and PL as follows:

Summary of Product Characteristics

[...]
4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of acute pain (see section 4.2)
~~Symptomatic treatment of painful osteoarthritis (see section 4.2)~~
Primary dysmenorrhoea

Nimesulide should only be prescribed as second line treatment. The decision to prescribe nimesulide should be based on assessment of the individual patient's overall risks (see section 4.3 and 4.4).
[...]

4.8 Undesirable effects
[...]

Gastrointestinal disorders
[...]
Uncommon: Gastrointestinal bleeding, Duodenal ulcer and perforation, Gastric ulcer and perforation
[...]
Hepato-biliary disorders
Common: Hepatic enzymes increased
[...]

Package Leaflet
[...]
1. WHAT *{(INVENTED) NAME}* IS AND WHAT IT IS USED FOR

{(Invented) name} is a non-steroidal anti-inflammatory drug ("NSAID") with pain-killing properties. It is used for the treatment of acute pain~~, for the treatment of symptoms of painful osteoarthritis~~ and for the treatment of period pains.
[...]

Figure 7 – Example of EC Recommendation Annex III, *adapted from reference (20)*

This recommendation is then evaluated and published by the EC. EC's decision shall be implemented by all member states.

In Portugal, INFARMED, I.P. will notify all MAHs, whose medicines are under the scope of EC decision, to submit product information texts accordingly. Deadline for submission is usually presented on the notification letter sent to MAHs.

For generic medicines nationally authorized, product information texts should be prepared similarly to those published by the EC for the innovative medicine, in the relevant areas (21). In order to facilitate the text adaptation process, INFARMED, I.P., dedicated a section of its website to the presentation of all referral procedures which are already concluded and their respective decision annexes, including the portuguese version of the product information texts (22). The first look of this website can be observed in figure 8.

Type of referral	Name	INN	therapeutic Group	Major Concerns	start of the procedure	Outcome	Date of Opinion	Date of Commission Decision	Conclusions/ SPC	Templates
Article 31 of Directive 2001/83/EC	Trimetazidina	Trimetazidina	3.5.1 Antianginosos	Avaliação do perfil benefício/risco	22-04-2012	Positivo com alterações ao RCM e FI e AIMs sujeitas a condições estabelecidas no Anexo IV da Decisão	21-06-2012	03-09-2012		
Article 30 of Directive 2001/83/EC	Zipos Zoref	Cefuroxima axetil	1.1.2.2 Cefalosporinas 2ª geração	Harmonização de RCM	20-04-2010	Positivo	24-05-2012	23-08-2012		
Article 30 of Directive 2001/83/EC	Flolan	Epoprostenol	4.3.1.4 Antiagregantes plaquetários	Harmonização de RCM	23-06-2011	Positivo	24-05-2012	08-08-2012		
Article 31 of Directive 2001/83/EC	Nimesulida	Nimesulida	9.1.7 - Aparelho Locomotor. Anti-inflamatórios não esteróides. Derivados sulfanilamídicos	Avaliação do perfil benefício/risco	19-01-2010	Positivo com alterações de RCM e FI Comunicação aos profissionais de saúde via DHPC	23-06-2011	20-01-2012		

Figure 8 – INFARMED, I.P.'s online information regarding referral procedures, *adapted from reference (22)*

Submission to INFARMED, I.P.

Since September 2005 the submission of type I variations of nationally authorized medicines must be done electronically, through an INFARMED, I.P.'s website application (23).

This online application has limited access to MAHs, since each one has an unique username and password, giving access to the all submission processes, both closed and under evaluation, of their authorized products.

Every time I needed to access this application, I had to go to INFARMED, I.P.'s website and choose the option *"Serviços Electrónicos"*, under *"Utilidades"* on the left side menu, as it is highlighted in figure 9.

Figure 9 – INFARMED, I. P.'s online access to electronic services, *adapted from INFARMED, I.P.'s website*

After left click on "*Submissão electrónica de alterações*" a new window opens and a login user and password are requested, as depicted from figure 10. These data are specific for each MAH, thus I needed to introduce the data accordingly to each client.

Figure 10 – INFARMED, I.P. online login to type I variation electronic submission, *adapted from INFARMED, I.P.'s website*

Once the login is completed, I was able to search all the variations submitted to any of the concerned client medicines and obviously to submit new variations, as demonstrated by figure 11.

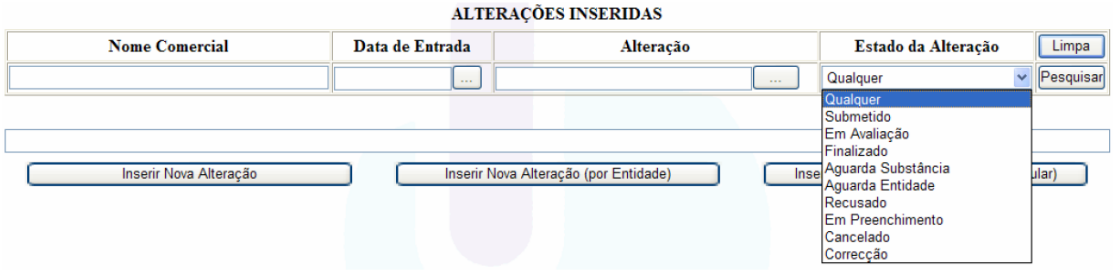


Figure 11 – INFARMED, I.P.'s online application for type I variations electronic submission: cover page, *reproduced from reference (24)*

Every time a new variation insertion starts a standard form, identical to the one presented in figure 12, has to be fulfilled regarding:

- Medicines identification (name, dosage and pharmaceutical form).
- Type of variation.
- Information regarding the submission of other variations.
- Goals of variation.
- Contact details of the person responsible for the submission.

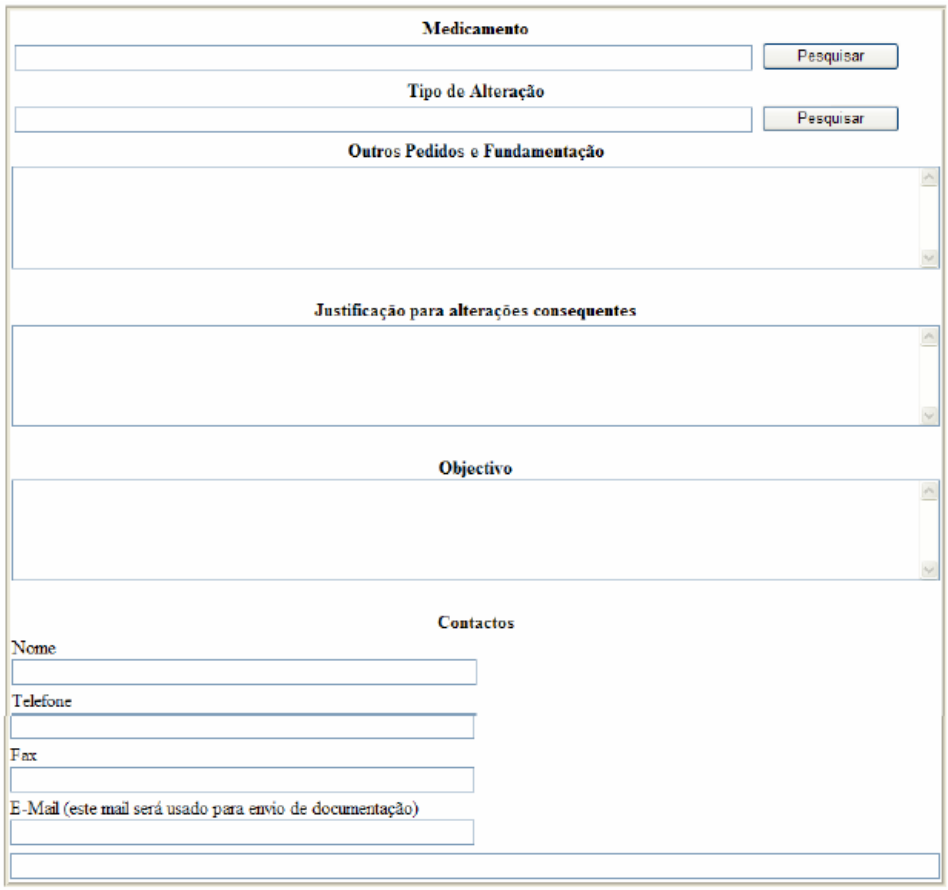
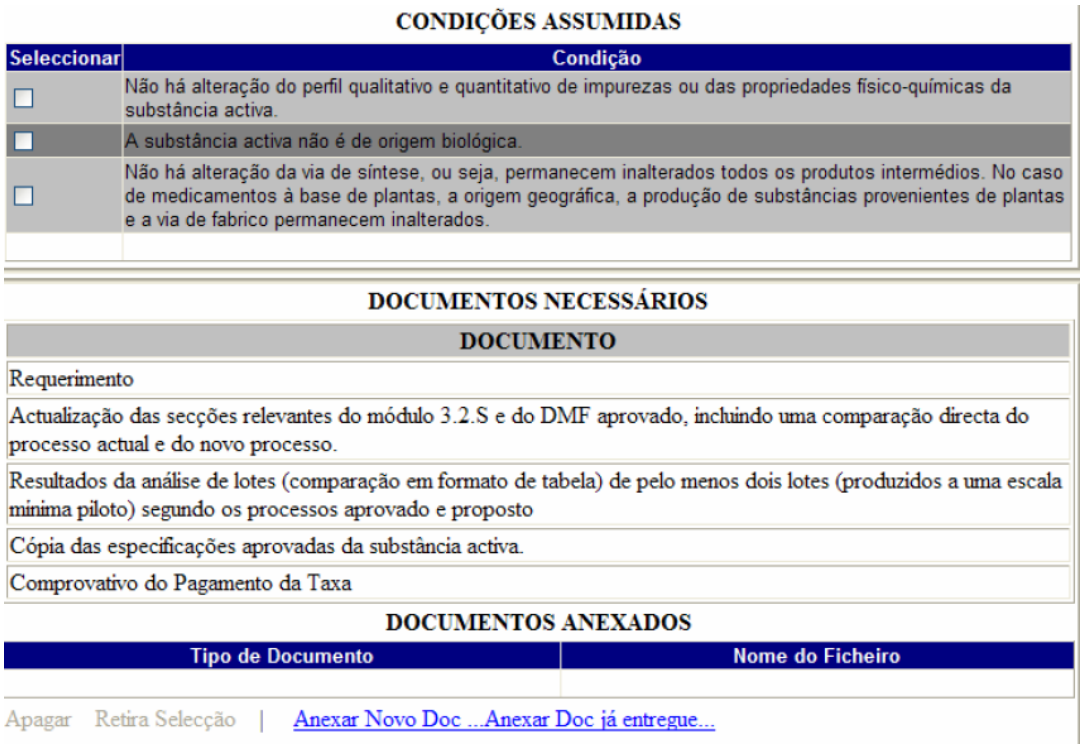


Figure 12 – INFARMED, I.P.'s online application for type I variations electronic submission: general form page, *reproduced from reference (24)*

As a result of the variation type previously chosen a variation specific form will show up in the next step of variation submission, listing:

- All the conditions that must be completed, so that MA can submit changes under the scope of type I variations. It is important to mention that all conditions must be confirmed, as a way to guarantee that they will not be neglected.
- The entire set of documents essential to support MA variation. All documents must be uploaded with the corresponding designation.

An example of this specific form is presented on figure 13.



CONDIÇÕES ASSUMIDAS

Seleccionar	Condição
☐	Não há alteração do perfil qualitativo e quantitativo de impurezas ou das propriedades físico-químicas da substância activa.
☐	A substância activa não é de origem biológica.
☐	Não há alteração da via de síntese, ou seja, permanecem inalterados todos os produtos intermédios. No caso de medicamentos à base de plantas, a origem geográfica, a produção de substâncias provenientes de plantas e a via de fabrico permanecem inalterados.

DOCUMENTOS NECESSÁRIOS

DOCUMENTO
Requerimento
Actualização das secções relevantes do módulo 3.2.S e do DMF aprovado, incluindo uma comparação directa do processo actual e do novo processo.
Resultados da análise de lotes (comparação em formato de tabela) de pelo menos dois lotes (produzidos a uma escala minima piloto) segundo os processos aprovado e proposto
Cópia das especificações aprovadas da substância activa.
Comprovativo do Pagamento da Taxa

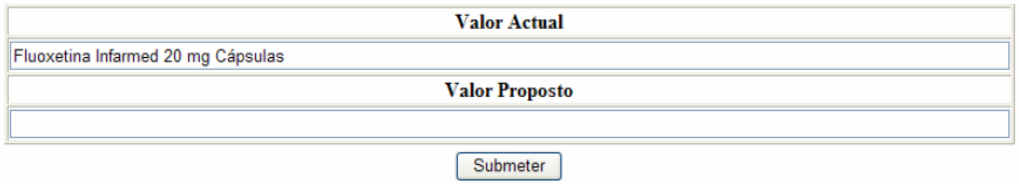
DOCUMENTOS ANEXADOS

Tipo de Documento	Nome do Ficheiro

Apagar Retira Selecção | Anexar Novo Doc ...Anexar Doc já entregue...

Figure 13 – INFARMED, I.P.'s online application for type I variations electronic submission: example of variation's specific form, *reproduced from reference (24)*

For some variations, INFARMED, I.P. also requests the identification of the currently approved information versus the proposed information disposed in the tabular format of figure 14.



Valor Actual
Fluoxetina Infarmed 20 mg Cápsulas
Valor Proposto

Submeter

Figure 14 – INFARMED, I.P.'s online application for type I variations electronic submission: specific form of currently approved versus the proposed information, *reproduced from (24)*

After completing all forms, the variation can be submitted and sent to evaluation. At this point I could not make any change to the information submitted.

Besides the access to type I variations, the INFARMED, I.P.'s online application for type I variations electronic submission also accomplishes a database of SmPCs and PLs. These versions must be used whenever a new variation with impact on SmPC and/or PL is submitted and for MA renewal requests. This obligation is applicable to all nationally authorized products since November 2006 (25). These versions available on INFARMED, I.P.'s online database have a special feature: all text changes and deviations from the approved version are registered as track-changes and it is not possible to unable this Microsoft Word's functionally, as it can be observed in figure 15.

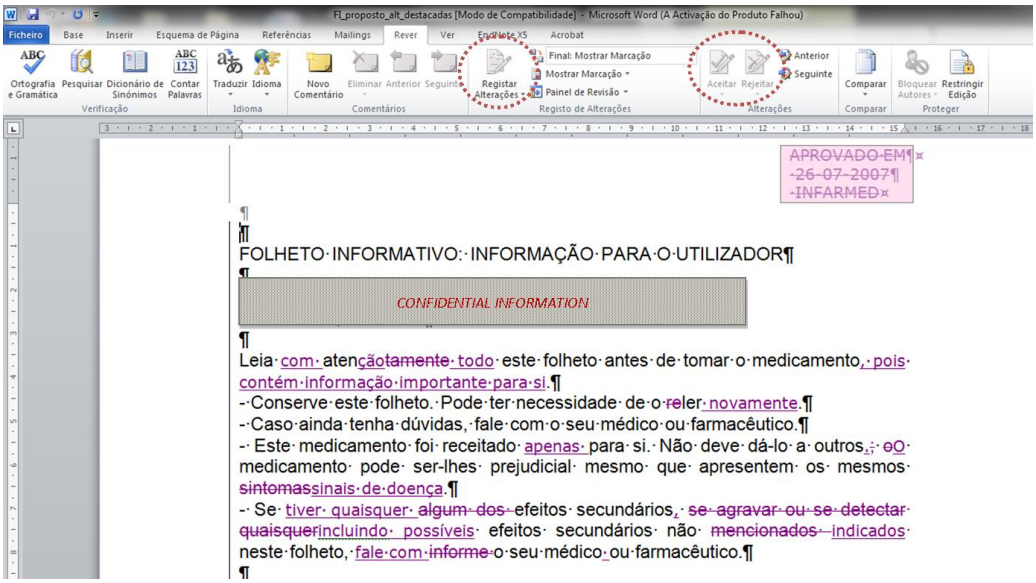


Figure 15 – Example of INFARMED, I.P.'s track change file for product information texts

Track-changes functionality is particularly important to INFARMED, I.P.'s variation managers, because it allows making an easy identification of the changes proposed and simultaneously avoid losing time comparing versions to find out if there are no other changes than those arising from the variation process.

Regarding type I variations, the new information introduced on track-changes documents cannot present other than the one resulting from the variation itself. The adaptation of texts templates to the latest version of QRD recommendations should be avoided, since texts evaluation will not be performed by INFARMED, I.P.. Additionally, from January 1, 2012 all product information texts (SmPC, PL

and/or labelling) submitted during variation procedures should implement the necessary changes to correct the text accordingly to the rules of the new orthographic deal (26).

Evaluation and Approval Timings

Type IA variations of nationally authorized products will be assessed by the portuguese national competent authority, INFARMED, I.P., within 14 consecutive days after its submission. If INFARMED, I.P. does not emit any decision within this period, variations will be considered tacitly approved (15).

On the other hand, type IB variations will be validated by INFARMED, I.P. within 5 days of submission date. Only then the evaluation period will start and it can take up to 30 days. Thus, a type IB variation can be considered as tacitly approved if there is no decision from INFARMED, I.P. for a period of 35 consecutive days after submission (15).

During the validation period INFARMED, I.P. will evaluate if the request complies with the applicable requirements. If nonconformities are detected, the applicant will be notified to complete or change the documentation submitted, so that the evaluation can proceed (15).

During the evaluation period of a valid variation request INFARMED, I.P., may also ask for the presentation of additional documentation in order to perform a more complete evaluation of the request. The new documentation should be present within the period established by INFARMED, I.P. (15).

The countdown for issuing decisions and tacit approval will be stopped from the day new documentation or information is requested, until its submission (15). In this context, it is very important to answer these element requests as soon as possible, so that the predicted date of approval is not too delayed. To accomplish this objective I used to include this type of task on my top priorities, unless otherwise indicated by MMD’s coordinator.

Additionally, variation requests will be refused if the requested information is not submit within the define deadlines (15). In these situations the applicant can

submit a new request considering the correction of the points that lead to a negative position from the authority.

Personal Experience: Modus Operandi and Principal Handicaps

During the 9 months internship, I prepared, submitted and made follow-up of approximately 34 different type I variations, as presented on table 2.

Table 2 - List of type I variation prepared and submitted during the internship

Variation Identification Number	Variation Description	Variation type	Estimated number of variation projects during internship
2	Change in the name of the medicinal product	IB	6
5	Change in the name and/or address of a manufacturer of the finished product	IA	1
7 a)	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Secondary packaging for all types of pharmaceutical forms	IA	1
7 b) 1.	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - Primary packaging site - Solid pharmaceutical forms, e.g. tablets and capsules	IA	1
7 c)	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product - All other manufacturing operations except batch release	IB	1
8 b) 2	Change to batch release arrangements and quality control testing of the finished product - Replacement or addition of a manufacturer responsible for batch release - Including batch control/testing	IA	1
9	Deletion of any manufacturing site (including for an active	IA	3

	substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place)		
15 a)	Submission of a new or updated European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance - From a manufacturer currently approved	IA	1
15 b) 2.	Submission of a new or updated European Pharmacopoeia certificate of suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance - From a new manufacturer (replacement or addition)	IA	1
29 a)	Change in the qualitative and/or quantitative composition of the immediate packaging material - All other pharmaceutical forms	IA	1
30 b)	Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier); spacer devices for metered dose inhalers are excluded - Replacement or addition of a supplier	IB	9
40 b)	Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative or quantitative composition and mean mass - All other tablets, capsules, suppositories and pessaries	IA	1
42 a) 1.	Change in: the shelf life of the finished product – as packaged for sale	IB	3
44	Change in the summary of product characteristics of an essentially similar product following a Commission Decision for a referral for an original medicinal product in accordance with Article 30 of Directive 2001/83/EC	IB	4

I consider important to outstand that for each type I variation identified on table 2, I had to follow all the requirements and procedures previously described, such as the preparation of documentation set, operating the INFARMED, I.P.'s online application for type I variations electronic submission, or answer to elements requests within the defined deadlines.

In general, the best method to start preparing a type I variation is to identify the feasible variation at the guidance note. After that it is important to make sure that all the conditions mentioned for the chosen variation are integrally respected. If so, it is then possible to start collecting and preparing all the documentation previously enumerated.

Notwithstanding the obligation to use the track-changes files for every variation of nationally authorised products, I should identify which file to use, because the version available at INFARMED, I.P.'s variations online application may not be the latest version in use. This important detail can be explained by the fact that new product information texts will be approved (i.e., stamped with INFARMED, I.P.'s approval imprint) only in case of type II variations or/and renewal processes. For all the other situations the changes made to the product information texts are approved and the new versions can be printed and normally used, however INFARMED, I.P. will not present new imprinted versions. As a consequence the versions available at Infomed (the portuguese database of medicines) and at INFARMED, I.P.'s online application for variations submission will remain the same until texts are fully evaluated and stamped with INFARMED, I.P.'s approval imprint.

The presented features may, in some cases, difficult the identification of the latest version of the SmPC and PL which embraces all the information referent to previously submitted type I variations. In this context, I established a sequence of steps to be followed in order to detect the latest SmPC and/or PL:

1. Identify the latest variations which had impact on product information texts.
2. Verify if the product information texts submitted on each variation, reflect all the previous variations.
3. If it is concluded that all the previous variations are reflected on the latest versions submitted, that documents can be used and the changes reflecting

the current variation should be included. On the contrary, if it is found out that the latest version submitted does not reflect all the variations previously submitted, the version under development should be drawn up to embrace all the changes on a single document, including those that did not result from the variation to be submitted.

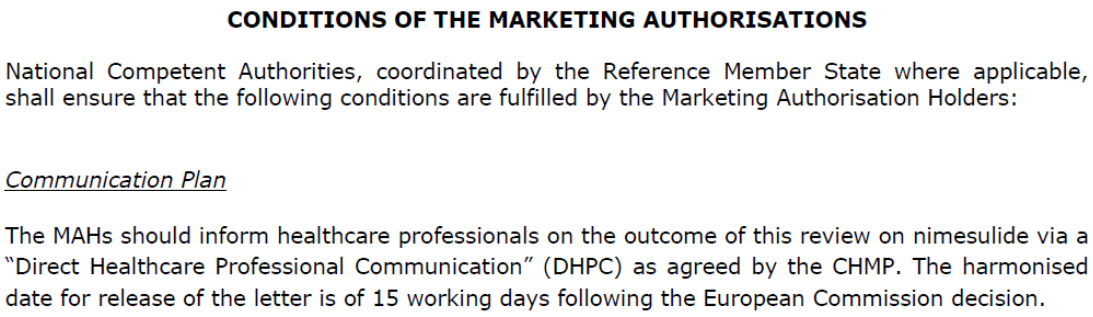
After submission, MA variation projects are in standby until there is an information request from INFARMED, I.P. or until the evaluation deadline is completed and tacit approval is granted. However, it is important to take in consideration that the end of the evaluation period does not necessarily represent the close out of the project. It is common that INFARMED, I.P. does not update the status of MA variation at the online application for type I variations electronic submission. In these situations I had to call to *Direcção de Avaliação de Medicamentos* (DAM), within the attendance periods (Tuesdays and Thursdays morning), to speak with INFARMED, I.P.´s manager responsible for the variation, in order to request the change of variation status to "*Finalizado".*

At this point, and in respect to Phagecon's usual procedures, I should make a print screen of the INFARMED, I.P.'s online application for type I variations electronic submission and archive it at the MA variation specific folder. This print screen works as proof of evaluation and authorisation from INFARMED, I.P., since approval certificates are not emitted for the most of type I variations. The status of project at Phagecon's Project Manager Software should also be updated and a notice notification should be prepared to inform client of the conclusion of the project. For medicines whose MAH is a company from the group (Laboratórios Basi, Overpharma, FHC, Empipharma or Paracélcia) variation history and their resulting documents should be updated on an online database named Online Regulatory Information on Medicines (ORIMED). ORIMED is a tool for internal management of regulatory information of each medicine and also a platform of interaction with the client, who access a restricted area through the clients' portal.

After gathering type I variation approval and if MA dossier is in e-CTD format, I should update the dossier on the e-CTD programme by the creation of a new sequence concerning a single variation. After validation, the new sequence shall

be recorded in non-rewritable CD-ROM and sent to INFARMED, I.P.. Since the variation is already approved, the information sent to INFARMED, I.P. is merely informative and no changes to the variation status will be possible.

At last, regarding referral procedures, I would like to highlight a particular case, due to the specificity and usualness of the processes required by the respective EC decision. Despite the usual changes to SmPC and PL, the EC Decision of nimesulide referral procedure also encompasses a communication to healthcare professionals, as described on its Annex IV – "Conditions of the marketing authorisations", which is presented on figure 16.



CONDITIONS OF THE MARKETING AUTHORISATIONS

National Competent Authorities, coordinated by the Reference Member State where applicable, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

Communication Plan

The MAHs should inform healthcare professionals on the outcome of this review on nimesulide via a "Direct Healthcare Professional Communication" (DHPC) as agreed by the CHMP. The harmonised date for release of the letter is of 15 working days following the European Commission decision.

Figure 16 – Example of Annex IV of an EC Recommendation regarding a referral procedure: the nimesulide case, *adapted from reference (27)*

Thus, each MAH of medicines containing nimesulide had to send thousands of letters (approximate 10.000 just for Portugal) to inform certain specialized healthcare professionals of the removal of painful osteoarthritis indication, new posology and contraindications (28). In reality, the compliance with this safety measure required a big logistic effort at Phagecon's and the enrolment of all the team so that the deadline could be accomplished. As a team, we started by organizing the different information letters from each of 12 MAHs in groups. After that we had to put each group of 12 notification letters on individual envelopes. The next step of work chain was pasting stickers with each healthcare professional name and address in all envelopes. The last task was to separate envelopes by the ZIP codes of the addresses on the stickers, so that this unusual volume of mail can be easily delivered on mail post.

Type II Variations

Overall Requirements

Any variation not specified in the guidance note for type I variations or that does not respect 1 or several conditions, should be classified as a type II variation (29).

Similarly to type I variations, there is also a board-spectrum set of documentation which I had to prepare in order to submit type II variations, including (15):

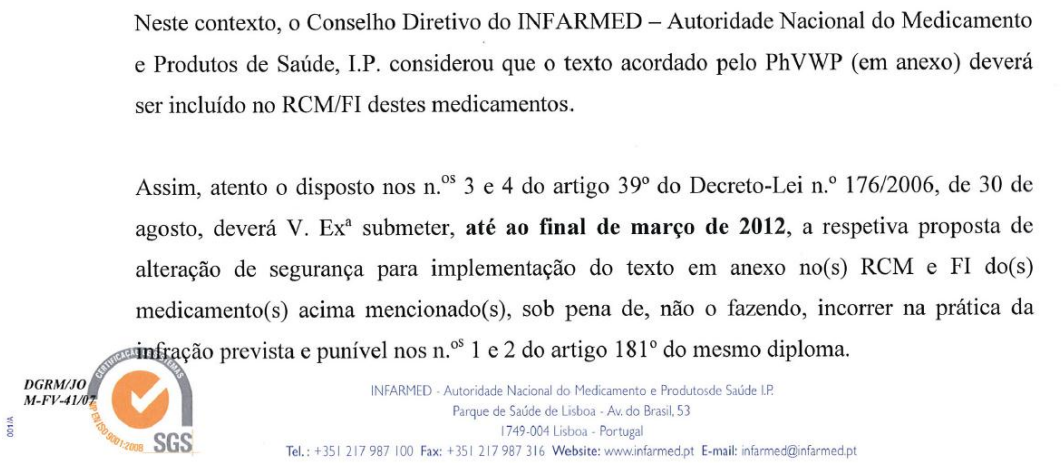
- Data supporting the request variation.
- Any document for which a new version had to be prepared as consequence of the proposed variation, including MA dossier updated sections and SmPC, RCM and/or labelling.
- Updated reports or experts evaluation of the proposed variation.
- Proof of payment of the applicable fees and the corresponding guide of payment duly completed.
- Identification of other MA variations already presented or to be presented in a near future, related to the same MA.
- Presentation of the deadline for the implementation of the proposed measures, specifically for safety variations.

Some of the information previously enumerated is requested to be presented in a specific form that should be completed and submitted for each type II variation. The referred form is applicable for nationally authorized products type II variations, and also for MRP and DCP approved products.

Similarly to type I variations, SmPC, PL and labelling documents must be submitted in INFARMED, I.P.'s track-changes versions. However, type II variations allow MAH to adapt SmPC and PL templates to the latest QRD versions. Track-changes from already approved variations should also be submitted and the new orthographic deal implemented (26).

There is a specific type II variation which is requested by INFARMED, I.P. and intends to update SmPC and PL as a mitigation measure of a potential risk or safety issue. These variations are commonly noun as type II safety variations and

are communicated to MAH trough a notification letter from "*Direcção de Gestão do Risco de Medicamentos*" (DGRM), similar to the excerpt presented on figure 17. DGRM is one of the INFARMED, I.P.´s specialized department specialized on the evaluation and minimisation medicines' risks.



Neste contexto, o Conselho Diretivo do INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. considerou que o texto acordado pelo PhVWP (em anexo) deverá ser incluído no RCM/FI destes medicamentos.

Assim, atento o disposto nos n.os 3 e 4 do artigo 39º do Decreto-Lei n.º 176/2006, de 30 de agosto, deverá V. Exª submeter, **até ao final de março de 2012**, a respetiva proposta de alteração de segurança para implementação do texto em anexo no(s) RCM e FI do(s) medicamento(s) acima mencionado(s), sob pena de, não o fazendo, incorrer na prática da infração prevista e punível nos n.os 1 e 2 do artigo 181º do mesmo diploma.

DGRM/JO
M-FV-41/07

INFARMED - Autoridade Nacional do Medicamento e Produtosde Saúde I.P.
Parque de Saúde de Lisboa - Av. do Brasil, 53
1749-004 Lisboa - Portugal
Tel.: +351 217 987 100 Fax: +351 217 987 316 Website: www.infarmed.pt E-mail: infarmed@infarmed.pt

Figure 17 – Example of DGRM's notification letter, *where PhVWP corresponds to Pharmacovigilance Working Party and RCM/FI to SmPC/PL*

The notification letter is usually directed to the pharmacovigilance responsible person and encompasses the identification of:

- Medicines affected by the request.
- Text changes to be implemented.
- Deadline for implementation and variation submission.
- Deadline for implementation of approved changes to the texts.

Submission to INFARMED, I.P.

All documentations related to MA type II variations should be submitted in electronic format. However, there are different submission processes on whether it is a common type II variation or a safety type II variation.

Therefore, whenever considering the submission of common type II variations, I should sent a registered correspondence to INFARMED, I.P.'s address, with the following components (30):

- 2 copies of documentation in electronic format (2 non-rewritable CD-ROMs).
- A requirement, in paper.
- The original and signed version of application form duly signed.

Every time an elements request is made during the validation process, all the information should be submitted in 2 new copies. However, if there is an elements request during the evaluation process, applicant shall submit only the information corresponding to the question received (30).

Furthermore, I should have in consideration that any CD-ROM sent to INFARMED, I.P. must be properly identified with (30):

- Medicine's name, dosage and pharmaceutical form.
- Applicant and MAH (if not the same).
- Variation type and identification of the request nature (initial request, answer to elements request).

To respect this last INFARMED, I.P. demand, I used to request CD-ROMs' covers preparation to the administrative department (AD). Thus, all the information considered necessary for the identification of CD-ROM was directly printed on each CD-ROM by the use of a specific printer. To avoid confounding CD-ROMs from different projects I preferred to record the documentation only after receiving the CD-ROM with the printed cover.

CD-ROMs content also has a proper organization that should be respected, in order to harmonize the disposition of information that is receive by INFARMED, I.P. and consequently raise evaluation efficacy rates (30). Thus, there are 2 folders that should be present on the opening of CD-ROM: "*Dossier de Gestão*" and "*Dossier da AIM*".

"*Dossier da AIM*" folder shall respect the CTD format, which will be analysed in detail on MA Renewals subsection of the present report. However, when considering type II variations, it is not necessary to prepare all CTD folders, but

rather only those affected by variation. In case MA dossier is in e-CTD format, the information should be submitted in the form of a new sequence. The validation reports of each sequence should also be recorded on the CD-ROMs.

On its turn, "*Dossier de Gestão*" encompasses all administrative documentation related to the variation, such as requirement, copy of DGRM's notification letter, proof of payment of applicable fees and the corresponding guide of payment duly completed or the variations form duly completed and signed.

On the other hand, since May 25, 2009, safety type II variations submission process must be done through an online application (31). This online application is very similar to the one already presented for type I variations. In this context, it will be presented a list of major differences trough the different process phases or statuses, rather than a detailed description of the application functionalities, as following:

- Requested – the variation is created by INFARMED, I.P. and not by applicant, who is limited to required documents upload and submission (32).
- Payment confirmation – Applicable fees payment is not made prior to submission. After complete all the forms and upload the necessary documents, I must request the emission of a bill note. At this point the process will be blocked, i.e. no more changes can be done either to the forms or to the documents uploaded. The bill note identifies the fee value to be paid, as well as a specific identification number that must be present on the descriptive of bank transfer. A single bill note should be requested for each medicine. After requesting bank transfer to MAH and obtaining the respective proof of bank transfer, I should confirm the payment on the online application (32), as it is highlighted in figure 18.

Figure 18 – Bill note request at INFARMED, I.P.'s online application for safety type II variations, *adapted from reference (32)*

- Payment validation – at this point INFARMED, I.P.'s accountability department will verify if the payment done is accordingly to the bill note. If everything is correct the variation status will change to "*Pagamento Validado*". After this, the variation is eligible to evaluation by DGRM's experts (32).

Evaluation and Approval Timings

Generally there are no defined timings for type II variations evaluation and approval. The exception is made for safety type II variations, which deadline for evaluation is usually present on the notification letter sent to MAH.

Regardless the different deadlines for evaluation, at the end of this process MAH will receive an approval letter which authorizes the proposed MA variations.

In case the variation comprised new product information texts, INFARMED, I.P. will present a new imprint version and update the versions available on Infomed and on type I variations online application.

During the evaluation process, element requests may be considered necessary by the DGRM expert responsible for evaluation. A deadline of 30 working days is given to answer the 1st elements request and a 2nd elements request can be answered within 10 working-days. Only the 1st elements request deadline can be

extended. Whenever considering safety type II variations, elements requests should also be answered through the online application, as indicated in figure 19.

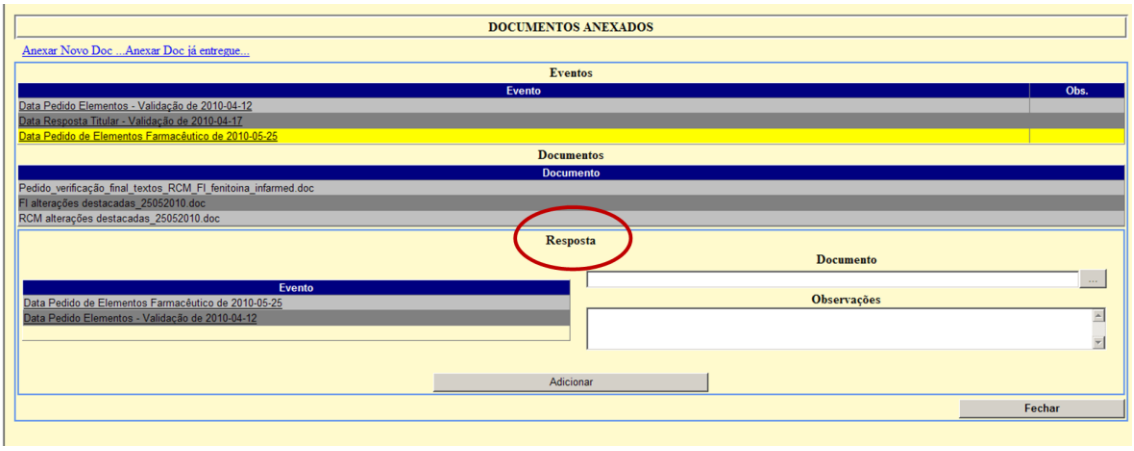


Figure 19 – Answer to element request at INFARMED, I.P.'s online application for safety type II variations, *adapted from reference (32)*

Personal Experience: Modus Operandi and Principal Handicaps

During the 9 months internship, I prepared, submitted and made follow-up of 2 type II variations and 3 safety type II variations.

Since there are substantial differences between safety type II variations and common type II variations that don not allow describing my personal experience in type II variations as a whole.

Therefore, and regarding the common type II variations preparation, the main hurdles were related to the definition of the documentation that should be submitted. Contrarily to type I variations there are no lists of document that shall be submitted. Thus, I had to think about the essential information for variation approval on a case by case basis. At this point, it was very useful for me to look at the most similar type I variation, because the documents listed on the guidance note are very likely considered essential for evaluation of type II variation and will have to be part of the documentation set submitted to INFARMED, I.P..

In which concerns to safety type II variations, there are no major difficulties to be pointed since the documentation to be submitted is predefined and the online

application to be used for submission is user friendly, making the submission process simple and institutive.

However there is one difficulty which cross-cuts all variation types (including type I, type II and safety type II) and even renewals: the identification of the latest version of the SmPC and PL, i.e. the version that embraces all the information referent to previously submitted variations, as previously explained on type I variations subsection. The reasons that explain this hardness, as well as mitigation strategies, were already discussed on type I variation subsection.

A type II variation project will be considered finalized after the reception of the approval letter from INFARMED, I.P.. After that, in respect of Phagecon's internal procedures, I should:

- Update the project status at Phagecon's online Project Manager Software.
- Prepare a notice notification to inform client of the conclusion of the project.
- Filed the original approval letter on the management dossier of the corresponding medicine and its scan on the electronic database, more specifically at the folder corresponding to the undertaken variations, existent at medicine's specific folder.
- Update medicine's variation history at ORIMED, in case MAH is a company from the group.

Transfer of Marketing Authorisation

Overall Requirements

Accordingly to EMA's definition a transfer of MA "is the procedure by which the MA is transferred from the currently approved MAH to a new one, who is a different person/legal entity" (33).

The request must be submitted by the current MAH and it should include all the following documents (15, 29):

- Document which identifies the medicine, the MA procedure number and the date MA was granted. Additionally other information considered relevant to medicines characterization, such as active substance, pharmaceutical form, registration number or dosage, may be added.
- Document which identifies the current MAH and the proposed MAH, including for each one the following information: name, address, contact person at the indicated address, telephone number and e-mail.
- A declaration certifying that the medicines' up-dated process and MA dossier will be given to the future MAH.
- A declaration stating the date from which the new MAH will assumed all responsibilities related to the medicine.
- Document with the identification and detail contacts of the future responsible for medicine's Pharmacovigilance activities. The signed and dated CV of the technical responsible for Pharmacovigilance should be annexed to the present declaration.
- Document with the identification and detail contacts of the future responsible for the scientific department and activities.
- Updated versions of SmPC, PL and labelling, with track changes.
- Declaration that assures that the only changes made to medicine's information texts are those that result from transfer of MA.
- Proof of payment of applicable fees and the corresponding guide of payment duly completed.

It is important to take in consideration that all these declarations should be properly signed by the current and the future MAHs' legal representatives.

Submission to INFARMED, I.P.

Submission to INFARMED, I.P. is made on a paper basis only. Thus, all original documents are organized and divided by cover pages in a single dossier.

The complete dossier is then sent as registered correspondence to INFARMED, I.P.'s address.

Evaluation and Approval Timings

INFARMED, I.P. will evaluate and emit a decision within 60 days of submission of a valid request (15). Thus, the process will be considered finalised after reception of INFARMED, I.P.'s approval letter and the new imprinted version of product information texts.

After approval, I had to follow all the Phagecon's internal procedures, previously describe for type I and type II variations.

Personal Experience: Modus Operandi and Principal Handicaps

During the 9 months internship, I had the opportunity to prepared and follow-up 6 transfers of MA.

At the moment of INFARMED, I.P.'s approval letter reception, I had to confirm all its content. If I detected any deviation, such as a wrong pharmaceutical form or dosage, I had to contact INFARMED, I.P.'s responsible manager, within attendance periods, to communicate the mistakes found and request a new approval letter with accurate information.

In general, transfers of MA are simple processes, which I accomplished without major difficulties apart from the narrow execution period of some cases.

Nevertheless concerning the current INFARMED, I.P.´s efforts to reduce bureaucracy and to develop friendly user electronic tools, I consider that MA transfer submission process could be update to a simpler and less administrative process, such as MA variations. In my opinion this could be easily done by the emission of a new "*Circular Informativa*" regarding the obligation of electronic submission in 2 non-rewritable CD-ROMs, despite the current dossier in paper format.

Marketing Authorization Renewals

Overall Requirements

All medicines under commercialization in EU must have a valid MA, granted by a european competent authority. However this authorization is usually granted for a certain period of time, after which MAH should submit a renewal request, if there is intention to continue to commercialize the medicine.

This section will give further details on MA renewal procedures for nationally authorized products, with special emphasis on the regulatory framework, the concert action and tasks to be performed and finally the major learning's and greatest hurdles I felt.

It should be noticed that, during the internship all the renewal projects that I had the opportunity to develop were from nationally authorized products, as a result, all the information to be present on this subsection is exclusively related to nationally authorized products and the applicable legislation for that period (August 2011 to May 2012).

The first MA granted to a certain medicine is valid for a period of 5 years. After that, and if there is interest in maintaining the medicine on the market, a renewal request should be submitted within the established timelines (15).

If the renewal request is approved, the second MA will be valid for an undetermined period, unless there are safety concerns that compel INFARMED, I.P. to define a new 5 years deadline for MA validity (15). This is particularly common in case of innovative medicines, which safety and/or efficacy profiles are not well noun.

Apart from the particularities of each MA renewal request, there is a set of documentation and information that I had to prepare for each renewal I submitted, namely (15, 34):

- A consolidated version of MA dossier, regarding safety, quality and efficacy. This consolidated version should include all changes introduced by all variations submitted and approved since the first MA.

- A description of medicine's pharmacovigilance relevant data, presented on a Periodic Safety Up-date Report (PSUR), specially prepared for the renewal purposes.
- Whenever applicable, any additional documentation that demonstrates the adaptation of medicine's related procedures (e.g. manufacturing) to scientific and technical advances.
- A set of relevant administrative information, such as: requirement, proof of payment of applicable fees and the corresponding guide of payment duly completed; renewal form; quality and clinical experts declarations; Good Manufacturing Practices (GMP); among others.

All these required documents must be presented accordingly to a well-established, which is based on 4 initial folders: "*Módulo 1"; "Módulo 2"; "Módulo 5" and "Dossier da AIM*", as it is presented on figure 20.

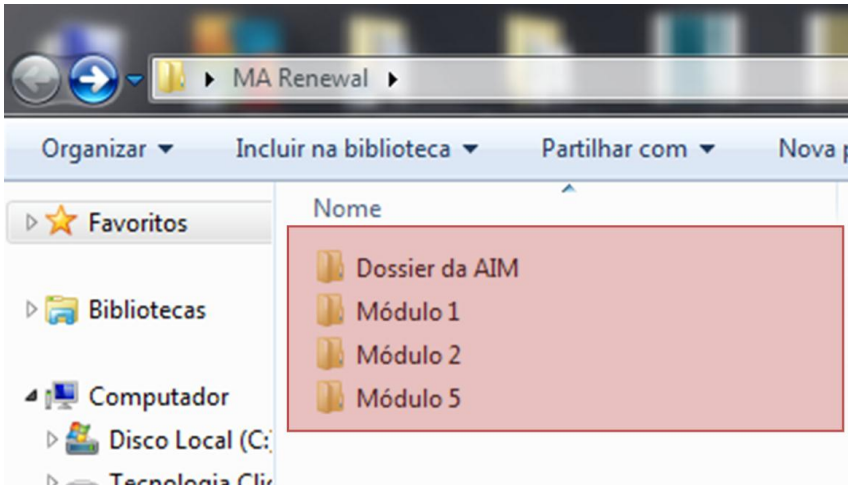


Figure 20 – MA renewal request: folder organization within submission CD-ROM

Inside "*Módulo 1*" folder there is also a highly structured organization for administrative documents disposal, which can be analysed in detail in figure 21.

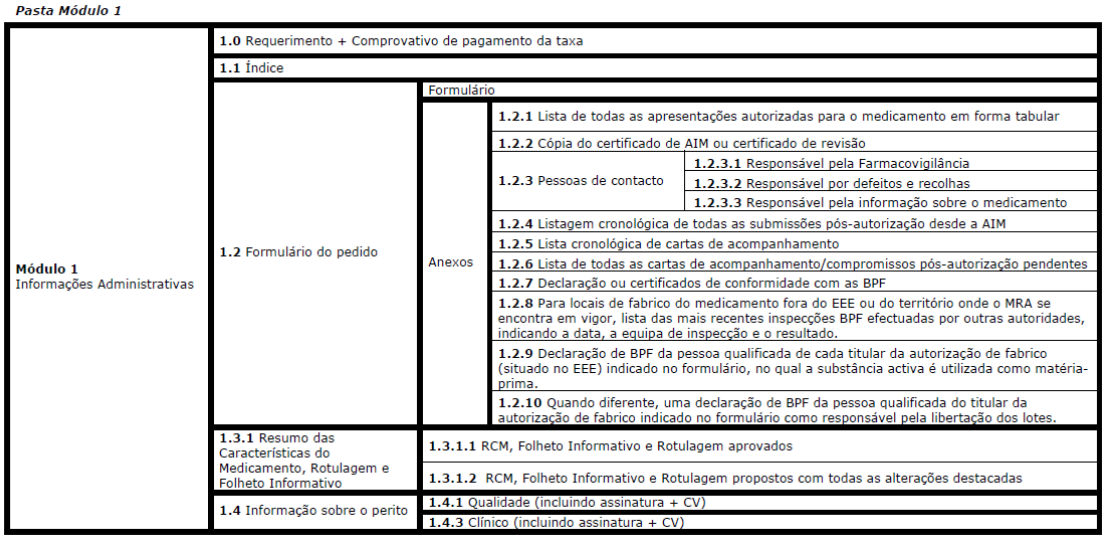


Figure 21 – MA renewal request: folder organization within "*Módulo 1*", *adapted from reference (35)*

There are several sub-folders of "*Módulo 1*", which deserve to be further analysed, such as section 1.2.7, where GMP certificates for all manufactures mentioned on MA dossier and renewal form (36). GMPs are not mandatory for active substance manufacturers, but whenever available they should be present on this section as well.

Regarding section 1.3.1.1, only the approved versions of SmPC, PL and labelling, i.e. those that have the INFARMED, I.P.'s imprint, should be considered. If it is not possible to have these documents with the referred imprint, a declaration should be added on this section. The declaration intends to confirm that, despite the absence of INFARMED, I.P.'s imprint, the approved and on use versions are those submitted in this folder.

On the other hand, the preparation of section 1.3.1.2 involves the development of new SmPC, PL and labelling versions, encompassing all the information from previously submitted and already approved or still under evaluation variations, which had impact on product information texts, as well as the latest QRD suggestions. As previously described on MA variations subsection, SmPC and PL are to be prepared on the track-changes documents.

Figure 22 presents the organizational structure of "*Módulo 2*" and "*Módulo 5*", which are in fact very simple, since it only embraces a couple of folders.

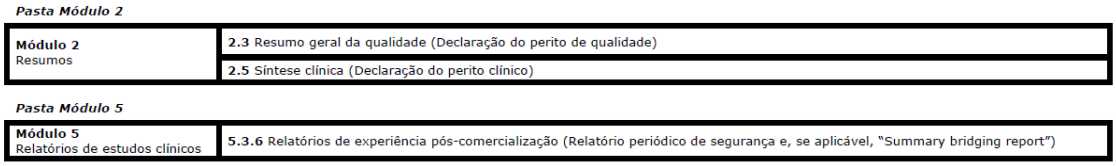


Figure 22 – MA renewal request: folder organization within "*Módulo 2*" and "*Módulo 5*", *adapted from reference (35)*

Quality and clinical experts declarations included on "*Módulo 2*" should respect the defined standards. Thus, quality expert's declaration should (37):

- Confirm that MAH respects the depositions of *Decreto-Lei 176/2006*, *de 30 de Agosto*, in which concerns to he/she obligation to track the scientific and technical progress of medicine's manufacturing and control processes.
- Assure that all quality related changes were introduced after the respective MA variation request approval by the competent authorities.
- Guarantee that the medicine manufacture and control processes are in accordance with CHMP current quality guidelines.
- Identify qualitative and quantitative composition of the medicine's active substance(s) and excipients.
- Confirm the currently approved active substance(s) and final product specifications.

On its turn, clinical expert declaration should describe medicine´s benefit-risk balance, based on the PSUR data and others collected since MA concession or last renewal. New and relevant information should be highlighted (37). By the mean of this declaration, clinical expert should also confirm that (37):

- There are no new data, both clinical and/or non-clinical, that could change benefit-risk evaluation.
- Medicine's MA can be renewed with safety. If the expert has a different opinion he/she should provide a justification and recommend safety measures accordingly.

- Competent authorities have been informed about any new and significant data to medicines benefit-risk evaluation.

On the other hand, "*Módulo 5*" is even simpler, since it will have a single document: the renewal PSUR. It is important to have in consideration that PSUR reporting period should match the renewal period. PSUR format and contents should respect the dispositions of Volume 9A – Pharmacovigilance for Medicinal Products for Human Use (the guidance in effect during the internship period) (36). No further details will be given on this particular matter because PSURs' preparation was not part of mine internship activities.

Finally regarding MA Dossier ("*Dossier da AIM*"), the first point to mention is that it should respect CTD format, either electronic (e-CTD) or note (folder structure). To avoid losing time preparing all folders and subfolders structure, MAH can download an empty CTD structure, as depicted from figure 23, from INFARMED, I.P.'s website.

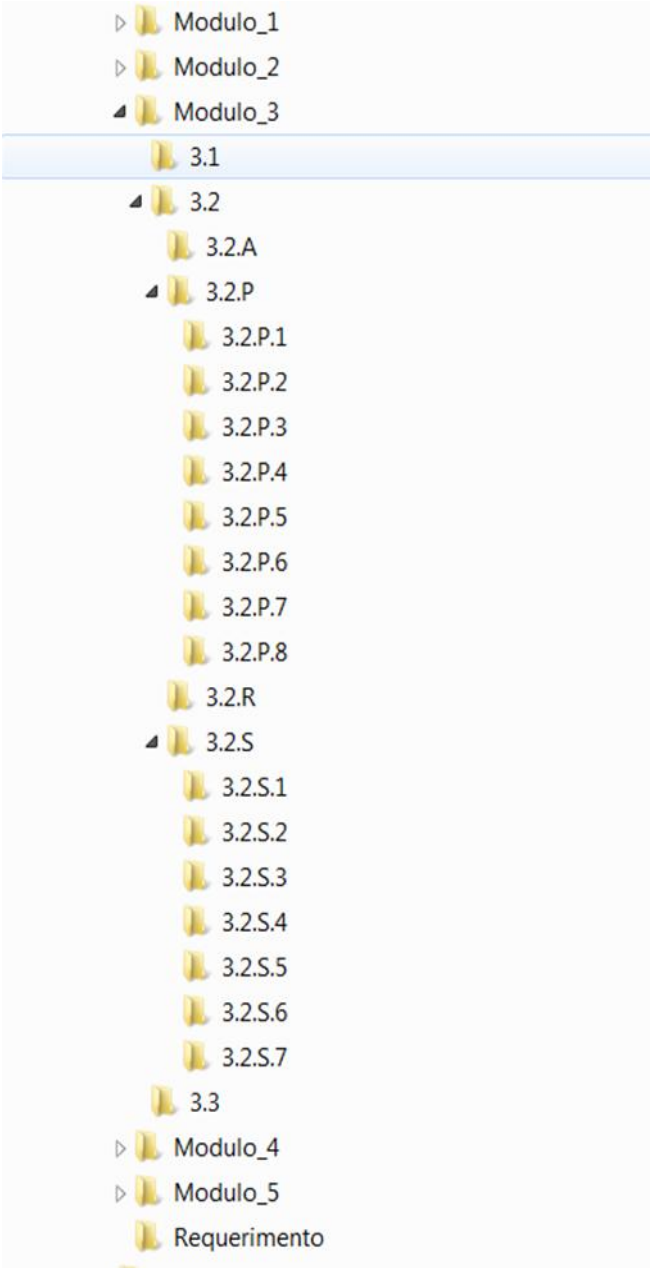


Figure 23 – MA renewal request: CTD folder structure for Module 3 of MA dossier

If there is more than one active substance manufacturer or more than one final product manufacturer, MAH can create more than one 3.2.S. or 3.2.P folders and identify them with the name of the corresponding manufacturer. It is important to notice that even with the duplication of these two folders their internal structure must be respect.

Submission to INFARMED, I.P.

As a way to ensure that all documentation essential for renewal request validation is submitted, it is sensible to read the INFARMED, I.P.'s check-list for renewal requests. In case missing documents are detected, they should be added before submission (36).

Renewal request submission must be done at least 180 days before the end of MA validity date, which is stated on MA certificated issued by INFARMED, I.P., as depicted from figure 24. It is important to take in consideration that this countdown will not start at expiry date stated on MA certificate, but rather on the day before that.

Ministério da Saúde

infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

CERTIFICADO DE
AUTORIZAÇÃO DE INTRODUÇÃO NO MERCADO

No cumprimento do artigo 26.º do Decreto-Lei n.º 176/2006, de 30 de Agosto, o Conselho de Administração do Instituto Nacional da Farmácia e do Medicamento certifica que foi concedida, por deliberação da data abaixo referida, a Autorização de Introdução no Mercado (AIM) para o medicamento abaixo indicado.

O titular da presente autorização deverá cumprir as disposições do Decreto-Lei n.º 176/2006, de 30 de Agosto, respectiva legislação complementar e demais normas aplicáveis.

A autorização a que se refere o presente certificado é válida por cinco anos, a contar da data abaixo referida, devendo ser solicitada a respectiva renovação até 180 dias antes do termo daquele período.

P/O CONSELHO DE ADMINISTRAÇÃO

Luísa Carvalho
Vice-Presidente do Conselho Directivo

Data de Autorização: 26 JUL. 2007

Figure 24 – MA renewal request: example of MA certificate emitted by INFARMED, I.P.

In case INFARMED, I.P. is closed on the day of renewal submission deadline, the request can be delivered the next working day.

If renewal request is not presented within the defined timelines as previously indicated, MA will expire. Furthermore, no extensions to the deadline for renewal procedures submission will be conceded (36, 38).

The renewal request must be submitted by mail to INFARMED, I.P.'s address and to the care of *Direcção de Avaliação de Medicamentos – Unidade de Manutenção no Mercado* (DAM-UMM). It should be presented on 3 non-rewritable CD-ROMs. The folders recorded on CD-ROMs have to respect the well-established organization, previously described (36).

Moreover, whenever preparing a MA renewal request submission I should had in consideration that any CD-ROM sent to INFARMED, I.P. must be properly identified with (36):

- Medicine's name, dosage and pharmaceutical form.
- Applicant and MAH (if not the same).
- Identification of procedure type (Renewal) and the submission date.

As previously described to type II variations, I used to request the CD-ROM cover preparation, i.e. the printing of the essential information, to AD.

Evaluation and Approval Timings

After submission, MAH will be informed via e-mail of the validation of their renewal request, as well as of the responsible project manager at INFARMED, I.P. (34, 37).

However, if it is detected that the request has missing documents or documents with lack of compliance to applicable legislations, INFARMED, I.P. will emit a single elements request – *validation elements request*. MAH will have 20 days to answer this elements request and deadline extensions will not be conceded by INFARMED, I.P. (36, 38). If MAH does not respond or if the response is considered unsatisfactory, a preliminary hearing will be schedule. During the preliminary hearing it will be possible to add new documents. If at this point MAH's answers still considered unsatisfactory or if preliminary hearing deadlines are not respected, MA revocation will be declared (34, 37). MAH will have 90 days to remove the affected medicine from the market. The 90 days countdown may start the day MA validity expires or any other date defined on INFARMED, I.P.'s revocation decision (36).

Every time an elements request requiring changes to submitted dossier is made during the validation process, all the information should be submitted in 3 new copies (36).

After renewal request validation, INFARMED, I.P.'s responsible manager will start the evaluation process based on risk-benefit relationship, in order to determine if the balance remains positive. During the evaluation phase MAH will have 30 working days to answer to a possible 1st elements request and 10 working days to answer a 2nd. MAH can ask for an extension of these deadlines twice, however the time deadline for 1st extension will not be superior to 30 or 10 working days, depending on whether it is related to the 1st elements request or the 2nd, respectively. In case it is necessary to ask for a 2nd extension request (at the end of 1st extension deadline), the extra time given cannot exceed half of the days conceded in the 1st extension (i.e., 15 or 5 working days) (36, 38).

At the end of process's evaluation, INFARMED, I.P.'s decision will be notified to applicant. In the granted MA notification letter's annexes it will be possible to found the approved versions of SmPC, PL and labelling with INFARMED, I.P.'s imprint.

On the other hand, if INFARMED, I.P.'s concludes that the benefit-risk relationship is no longer positive, a new MA will not be conceded. MAH will have 10 or 90 days to remove its medicine from the market, depending on the reason that lead to MA withdrawn. Days countdown may start at day MA validity expires or any other date defined on INFARMED, I.P.'s revocation decision (36).

Personal Experience: Modus Operandi and Principal Handicaps

From all the projects I had the opportunity to participate or develop at Phagecon, MA renewal request were the more complex, either because of the nature of some of the tasks involved either due to the need of planning well in advance.

Nevertheless, the experienced gained from the 5 MA renewal submissions I prepared and submitted, allowed me to gradually gain more experience and consequently the ability to work more independently.

In respect to the legislative framework (previously described) and Phagecon's internal procedures, there is a set of tasks with defined timelines that I had to respect whenever preparing a renewal project.

Thus, approximately 4 months before submission deadline, it is necessary to make a critical analysis of MA dossier and the variations submitted, in order to determine which sections need to be updated. Then I had to request the information necessary to make this update to the respective MAH.

At this point the project will be in stand-by until there is an answer from MAH. When the requested information is finally received I should confirmed if it is only a recent version of the already approved dossier or if in fact it is different information that do not respect the approved MA dossier contents (e.g. a new specification test). If I found out that there it is non-approved information, I should notify MAH that a new variation process concerning this information should be submitted before renewal submission. If MAH agrees, I should prepare and submit the variation as soon as possible. This step is extremely important because MA renewals should be used to present information updates only (e.g. recent active substance analyses certificates), rather than opportunities to present different information not previously evaluated.

The analysis of the set of received information also allowed determining if it would be necessary to make a second information request to MAH or not.

Independently from the decision taken it is now possible and highly advisable, to start to consolidate MA dossier, considering not just the new information received but also the variations submitted. During this process, the section with higher level of changes was, generally, the "*Módulo 3*" - Quality.

It may be useful to simultaneously request clinical and quality experts to prepare and send the respective declarations, in order to guarantee that these documents are made available on time.

At last, I had to prepare the administrative modules ("*Módulo 2*"; "*Módulo 3*"; "*Módulo 5*"), including all the applicable form and its annexes.

Despite the presentation of renewal related tasks as chronologic events it does not necessarily mean that they cannot be performed simultaneously. Indeed the

greater the number of tasks performed before renewal deadline is too close, the better.

Multilingual Notifications

Overall Requirements

In some situations, MAH may have interest on the commercialization of the same medicine in several countries, trough big international wholesalers like FHC. This compels us to the ideal scenario: to have a single PL and labelled package containing all the official languages of countries where it is going to be commercialized, so that the same production line is established and used no matter the destination country.

INFARMED, I.P. approves product information texts in portuguese, which should be used exactly as presented on the approved versions. Thus, if there is the intention to add a translation to other languages of the approved texts, it will be necessary to submit to INFARMED, I.P. a variation of labelling and PL not related to SmPC information. This type of variation is commonly noun as multilingual notification.

The documents necessary to submit a multilingual notification to INFARMED, I.P. are:

- Approved labelling and/or PL (QRD format).
- Proposed labelling and/or PL with track changes (QRD format).
- Proposed labelling and/or PL without track changes (clean version in QRD format).
- Declaration ensuring the equivalence between the Portuguese version and its translations.
- Final artworks of the proposed versions.

Submission to INFARMED, I.P.

To submit a multilingual notification, MAH should send to INFARMED, I.P.'s address the paper versions of the previously identified documents.

The proposed versions will be tacitly approved, if there is no INFARMED, I.P. decision within 90 days of its submission.

Personal Experience: Modus Operandi and Principal Handicaps

For the several multilingual notification projects received during the internship, the first step I took was to request a draft translation of the latest PL approved version to Phagecon's translation expert.

Simultaneously, I could start preparing the labelling QRD version, if not already available, and to analyse the sections to be updated, accordingly to QRD latest templates. I should also prepare the labelling translation in QRD format, with special attention to the standard terms and phrases that must be used.

After the reception of PL translated version, I had to perform a technical validation, especially regarding QRD terms, clinical terms and standard terms, using Medical Dictionary and EDQM database, respectively. The revised version will be send to MAH for artworks development.

The process will be in standby until artworks reception. Before submission, I had to analyse the artworks documents to confirm its contents and readability standards. If it is considered that mock-ups should suffer any alteration, the respective comments were introduced on the document and sent back to MAH. At the time of mock-ups' second version reception, I used to do a new verification in order to ensure that all the comments were correctly implemented. This process could be repeated several times until the final version was achieved. When mock-ups final version was available the process could be submitted to INFARMED, I.P..

As already described for other regulatory processes, after approval there is a set of tasks that should be accomplished, namely: Project Manager updating and project close-out, ORIMED update (whenever applicable), archive of documentation on the network, and communication to client of notification approval.

Veterinary Medicinal Products

A VMP is defined by the applicable legislation as: “any substance or combination of substances presented as having properties for treating or preventing disease in animals; or any substance or combination of substances which may be used in or administered to animals with a view either to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis” (39).

This chapter intends to describe all the VMP related activities that I developed during the first months of internship to a temporary client, who outsourced quality services to Phagecon. The main activities performed during this period were: MA renewals, MA variations, PSUR’s fees payment and mock-ups revision.

Marketing Authorisation Renewals

Overall Requirements

Similarly to already the described for human medicines, no VMP shall be placed on the European market before a MA is granted by a recognized competent authority. This MA also has a validity of 5 years, after which MAH should submit a renewal request, if he intends to keep the medicine on the market. Also similarly to human medicines, once the MA renewal is granted it will be valid for an undetermined period of time, unless there are safety concerns that lead competent authorities to establish another 5 years period (40).

MA renewal request should present the following documents/information (40):

- Consolidated version of all new all documents and information regarding VMP’s quality, efficacy and safety and variations submitted since first MA.
- Updated version of product information texts.
- PSUR.
- Whenever applicable, additional documents that proof the adaption to technical and scientific progresses.

- Proof of payment of the applicable fees.

The renewal request cannot include any new variation. If a MA variation is considered necessary, it should be submitted accordingly to the applicable procedures.

DVG may request at any time additional documentation, considered necessary to make an accurate judgment of benefit-risk balance(40).

MA will expire, if the medicine is not commercialized for a period of three consecutive years. These 3 years count even if the medicine had never been commercialized after first MA was granted. A new counting will start whenever there is a MA transfer (40).

Submission to Direcção-Geral de Veterinária

The deadline for renewal request presentation is the same as for human medicines, i.e. at least 180 days before MA validity date which is indicated on MA approval letter.

All the documentation should be submitted in electronic format, in CD-ROM or DVD. Exceptionally, the original versions of proof of payment of applicable fees, renewal form and requirement should also be submitted in paper format (41).

The electronic support should be well identified with the following information (42):

- Name of VMP and its target species, if essential to avoid confusion with other products.
- Type of application (i.e., renewal).
- MAH's identification.
- Version and the respective date.
- If there is more than one support to identify them, such as 1/3, 2/3 and 3/3.

The organization of files on CD-ROM followed the one proposed by the client and presented on figure 25.

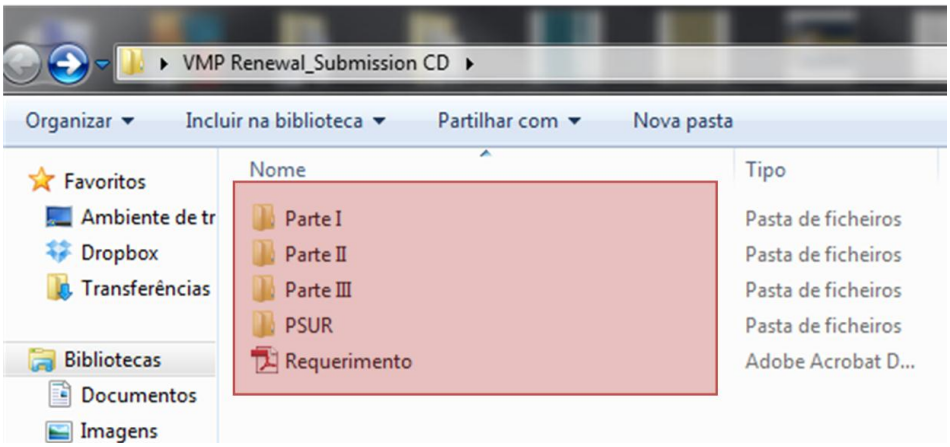


Figure 25 – VPM MA renewal requests: CD-ROM folder organization

"*Parte_I*" folder contains the renewal form duly completed and other relevant administrative documents, such as GMPs from manufacturers or experts' declarations.

On its turn, "*Parte_II*" should contain proof of payment of renewal fee. Finally "*Parte_III*" should present all the updated documentation that constitutes MA dossier.

Files are usually submitted in PDF format, with exception to the proposed versions of VMP information texts, which are prepared in word format. These documents should respect QRD format and present any change to the approved version on the track-change format, despite the fact that there is no specific document with this functionality, such it was described for human medicines. The clean version, i.e. without track-changes should also be presented (41).

For both submission and answer to elements request only 1 copy is required (41).

Evaluation and Approval Timings

During MA renewal request assessment, competent authorities will determine whether the benefit-risk balance remains favourable. The final decision will be taken by DVG director-general, after considering *Grupo de Avaliação de Medicamentos Veterinários* (GAMV) opinion and position (40).

The decision will be reported to MAH within 120 days after submission of a valid request. The approval letter encompasses also the approved versions of VMP information texts (40).

After renovation MA will be valid for an undetermined period of time, unless otherwise described on the approval letter. The obligation to submit a new renewal request within another 5 years will be assigned (40).

At last, all the decisions will become public trough the publication on DGV's website (43).

Personal Experience: Modus Operandi and Principal Handicaps

During the internship I had the opportunity to prepare and submit a single MA renewal, which MA dossier update was prepared by the client. Thus my responsibility was exclusively related to the administrative part of the process, which included: the preparation of the suggested files structure; the calculation of the applicable fees and their payment request and finally the submission to DGV by regular mail.

In this context, the major difficulties were to correctly identify the fee that should be paid, as well as DGV's submission requirements. The questions that could not be clarified trough the search on applicable legislation were asked directly to DVG via phone. Indeed, this was a very good solution, since all experts are extremely friendly and glad to help.

Marketing Authorization Variations

Overall Requirements

MAH should request for an authorization whenever he wishes to introduce changes to the approved information, so that it is possible to guarantee that all activities are performed accordingly to the applicable legislation and the validated scientific methodologies (40).

This subsection intends to describe the procedures associated to VMP MA variations that I undertake during the first internship months. Most of the activities performed were related to documentation preparation, since the submission was completed by the client (MAH).

Alike previously described for human medicines, MA variations of VMP are also classified, accordingly to their impact on the approved information, in:

- Type IA.
- Type IB.
- Type II.

The classification rules for national variation procedures, corresponding to those I developed during the internship, are detailed at DVG guidance "*Normas referentes às alterações aos termos das autorizações de introdução no mercado por procedimento nacional*" and at European guidance "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".

European guidance also establishes different variations within each type and organizes them in 3 different categories (44):

A. Administrative Changes
B. Quality Changes
C. Safety, Efficacy, Pharmacovigilance Changes.

For each variation, the European guidance also identifies the conditions that should be respected and also the specific documents that should be submitted, as presented in figure 26.

A. ADMINISTRATIVE CHANGES

A.1 Change in the name and/or address of the marketing authorisation holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA_{IN}
Conditions			
1. The marketing authorisation holder shall remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			
2. Revised product information.			
A.2 Change in the (invented) name of the medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) for Centrally Authorised products	1	1, 2	IA_{IN}
b) for Nationally Authorised Products		2	IB
Conditions			
1. The check by the EMEA on the acceptability of the new name has been finalised and was positive.			
Documentation			
1. Copy of the EMEA letter of acceptance of the new (invented) name.			
2. Revised product information.			

Figure 26 – VPM MA variation requests: excerpt from european guidance on VMP MA variations classification

Despite the need to present specific documentation to each type I variation, as outlined by European guidance, there is a general set of information that should be presented to DGV's Director-general, including (40, 41):

- Documents regarding the submitted variation, as well as the consequent updated version of MA dossier.
- Comparative table with currently approved information and the proposed by the variation. A declaration assuring that no other changes have been done besides those identified on this table should be annexed.
- Proof of payment of applicable fees.
- Identification of other variations submitted and under DGV evaluation or to be submitted on a near future.
- Updated versions of VMP information texts, whenever the variation has impact on them.
- Variation form duly completed.

- Requirement directed to DGV's director-general.

In case of type IA variations, the implementation date should be presented (45).

The applicable fees for type I variations and other VMP regulatory procedures are well described in portuguese law at "*Portaria n.º 27/2011 de 10 de Janeiro*". This document should be consulted were calculating applicable fees, since there is no guide of payment as for human medicines.

Submission to Direcção-Geral de Veterinária

All the documentation should be submitted in electronic format, in CD-ROM or DVD. Exceptionally, the original versions of proof of payment of the applicable fees, variation form and requirement should also be submitted in paper format (41).

The electronic support should be well identified with the following information (42):

- Name of VMP and its target species, if essential to avoid confusion with other products.
- Type of application (i.e., type IA variation or type IB variation and their respective identification number in accordance with European guidance).
- MAH's identification.
- Version and the respective date.
- If there is more than 1 electronic support, it will be necessary to identify each one of those, such as 1/3, 2/3 and 3/3.

Files organization on CD-ROM followed the one proposed by the client and it is presented on figure 27.

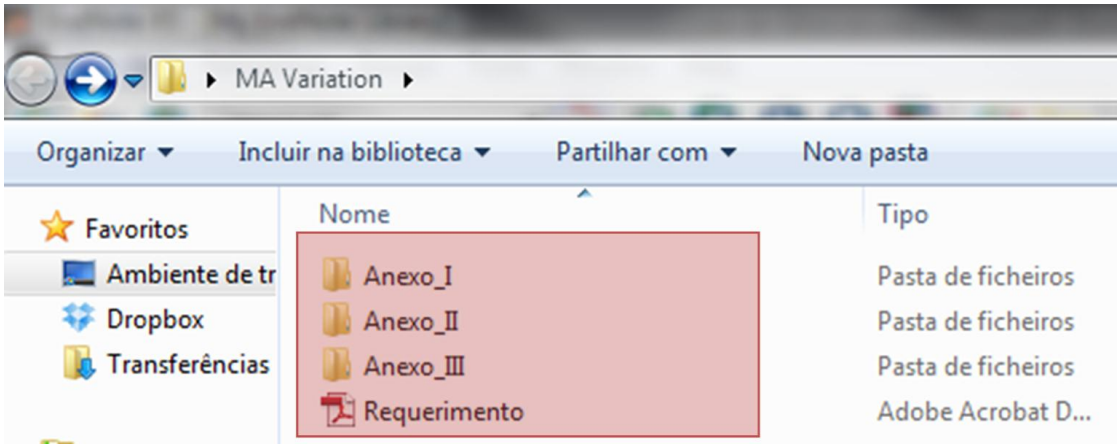


Figure 27 – VMP's MA variations CD-ROM structure: folder organization

The "*Anexo_I*" folder should contain the variation form duly completed. On its turn "*Anexo_II*" should contain fee variation proof of payment of variation fees. And finally "*Anexo_III*" should present all documentation which supports the variation, as well as the updated versions of MA dossier, whenever applicable.

Files are usually submitted in PDF format, with exception to the proposed versions of VMP information texts (whenever applicable), which are prepared in word format. All the changes made to the approved version of VMP information texts, should be presented as track changes. Additionally a clean version should also be submitted (41).

Regarding the number of copies that should be submitted, it is important to have in consideration that they vary accordingly to the type of procedure. Thus, for type IA variations 1 electronic copy is enough. However, for type IB variations, 2 electronic copies should be submitted. Whenever there is an element request from the authority, the answer should be submitted in duplicate, i.e. 2 CD-ROMs or DVDs should be submitted (41).

Evaluation and Approval Timings

The approval or refusal of MA variations is emitted by DVG's Director-general, after considering GAMV opinion. Minor type IA variations are an exception, since

they are usually not evaluated by GAMV, unless otherwise requested by Director-general (43).

In case of variation rejection or refusal, the reasons that lead to that decision will be properly identified and explained to MAH on the notification letter (45).

The periods defined for evaluation of VMP type I variations are similar to those applicable to human medicines. Thus, a type IA variation will be evaluated by DGV's Director-general within 14 days of its submission. If within this period there are no comments or emission of a variation refusal decision, it can be considered tacitly approved (40). It is important to notice that, despite the obligation to submit type IA variations, their implementation can be done even before the tacit approval (45).

The same is not applicable to type IB variations, which can be considered tacitly approved, if within 30 days after its validation by DGV, DVG's Director-general has not emitted a refusal communication (40).

Variations concerning only changes to labelling and/or PL, which are not related to SmPC information, will be considered tacitly approved, if DGV does not request additional information or if a communication regarding variation refusal is not emitted within 30 days of its submission (43).

The countdown for tacit approval is stopped whenever DVG requests for additional information or corrections to the documents previously submitted, such as product information texts. The variation request will be considered refused, if the applicant does not answer to DGV's questions and appeals within 30 days (40).

Personal Experience: Modus Operandi and Principal Handicaps

The great majority of projects developed in this area did not require the preparation of variation support documentation, because they came finalized from the client. Additionally, several variation projects did not achieve the submission phase, because it was performed by the client. In this context of limited action, there were no major difficulties, since the activities carried out were very similar to the ones performed for human medicines' variations projects. Some of the activities performed were: variation classification, the calculation of applicable fees

and the request of its payment by the client, the requirement preparation, or the update of VMP information texts.

Periodic Safety Update Report's Fees Payment

Overall Requirements

PSURs are documents intended to analyse the benefit-risk relationship of a VMP, based on knowledge acquire during the commercialization phase. They should encompass the worldwide safety information for a certain VMP, during a well-defined period on time (46).

The present section intends to describe the activities developed after PSURs submission, more specifically the contact with the competent authority and also the fee payment procedures. PSUR's preparation and submission were not part of this internship's activities.

PSURs should mention all ADRs in animals and humans occurred both in EEA and third countries, which MAH become aware of. Special attention should be given to new information arisen during the period cover by PSUR (46).

It is essential that PSURs encompass a scientific evaluation of benefit-risk balance, in order to determine if it remains positive or if there are new risks that require safety measures (40).

PSUR should be updated and submitted periodically, accordingly the following predefined intervals (40):

- Every six months since MA is granted until VMP commercialization.
- Every six months during the first 2 years of commercialization.
- Annually during the 3rd and 4th years of commercialization.
- Whenever a renewal request is submitted.
- Every 3 years after 1st renewal approval.

Additionally, PSUR should also be submitted whenever requested by the competent authorities.

PSUR has a well-defined structured which should be totally respected. Further details on this topic can be consulted at DGV's website (http://www.dgv.min-agricultura.pt/portal/page/portal/DGV/genericos?generico=201325&cboui=201325) , particularly at "*Instruções de Elaboração de Relatórios Periódicos de Segurança*" guidance document.

Personal Experience: Modus Operandi and Principal Handicaps

After receiving a new PSUR (directly submitted by the client) DVG sends an e-mail requesting the payment of the applicable fees.

Based on this e-mail a sequence of tasks should be undertaken, in order to answer the competent authority request. These tasks are sequentially presented below:

1. Determine fee value based on the analysis of "*Portaria n.º 27/2011 de 10 de Janeiro*". It is also useful to read the guidance "*Taxas de Submissão de RPS de Medicamentos Veterinário Nacionais, de Reconhecimento Mútuo, Descentralizados ou do Projecto de Partilha* ("WS")", available at DGV's website, because it describes real examples of law application, so that it becomes easier to understand and to use.
2. Sent payment request to the client, with clear identification of the value to be paid, the identity and the corresponding VMP and procedures.
3. Reception of fee payment proof and data verification.
4. Sent to DGV, via e-mail, the payment proof of applicable fees to the concerned PSUR.

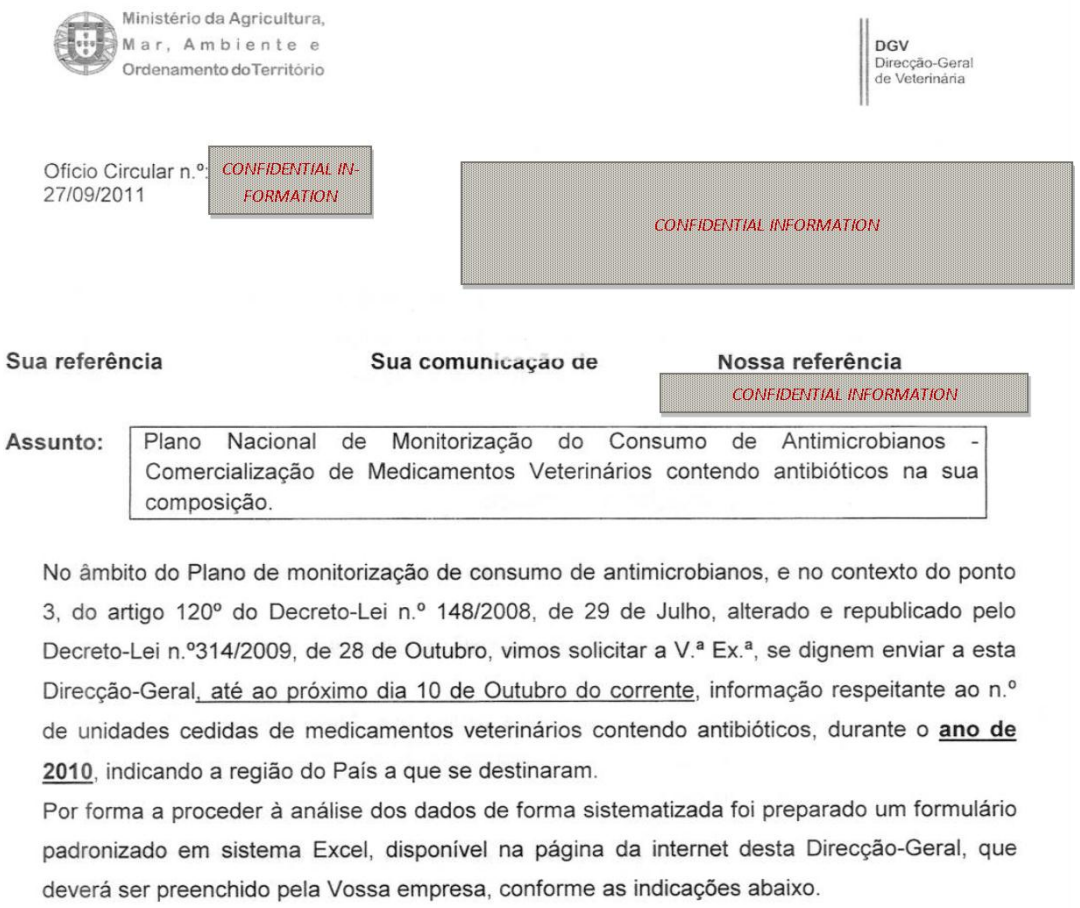
This was a very simple and mostly administrative activity that raised no issues.

National Monitor Plan for Veterinary Antimicrobial Consumption

DGV prepares annually a plan for the control of VMP use in food-producing animals, in order to verify if the using conditions respect the applicable legislation (40).

Lately there has been an increase of antimicrobial resistance in bacteria from animal production sites. This may lead to serious public health problems, leading EU to create the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), which intends to monitor veterinary antimicrobial consumption trends (47).

In this context, regarding the analysis of antimicrobial consumption in Portugal, DGV requested to MAHs and retailers information regarding the sales volume for VMP containing antimicrobials on its compositions, trough notification letters similar to the one presented on figure 28.



Ministério da Agricultura, Mar, Ambiente e Ordenamento do Território

DGV
Direcção-Geral de Veterinária

Ofício Circular n.º: CONFIDENTIAL IN-FORMATION
27/09/2011

CONFIDENTIAL INFORMATION

Sua referência	Sua comunicação de	Nossa referência
		CONFIDENTIAL INFORMATION

Assunto: Plano Nacional de Monitorização do Consumo de Antimicrobianos - Comercialização de Medicamentos Veterinários contendo antibióticos na sua composição.

No âmbito do Plano de monitorização de consumo de antimicrobianos, e no contexto do ponto 3, do artigo 120º do Decreto-Lei n.º 148/2008, de 29 de Julho, alterado e republicado pelo Decreto-Lei n.º314/2009, de 28 de Outubro, vimos solicitar a V.ª Ex.ª, se dignem enviar a esta Direcção-Geral, até ao próximo dia 10 de Outubro do corrente, informação respeitante ao n.º de unidades cedidas de medicamentos veterinários contendo antibióticos, durante o **ano de 2010**, indicando a região do País a que se destinaram.

Por forma a proceder à análise dos dados de forma sistematizada foi preparado um formulário padronizado em sistema Excel, disponível na página da internet desta Direcção-Geral, que deverá ser preenchido pela Vossa empresa, conforme as indicações abaixo.

Figure 28 – DGV's notification letter for the submission of antimicrobial consumption in Portugal during 2010

The information should be introduced on a specific Excel document, depicted from figure 29, which was specifically developed by DGV for this purpose, allowing the standardisation of it presentation by different MAHs, which will contribute to an easier and more efficient analysis.

Thus, the information regarding sales volume will be organized by medicine, in the first column, and by portuguese district, in the last column. The unique column of free answer is the one regarding the number of packages sold.

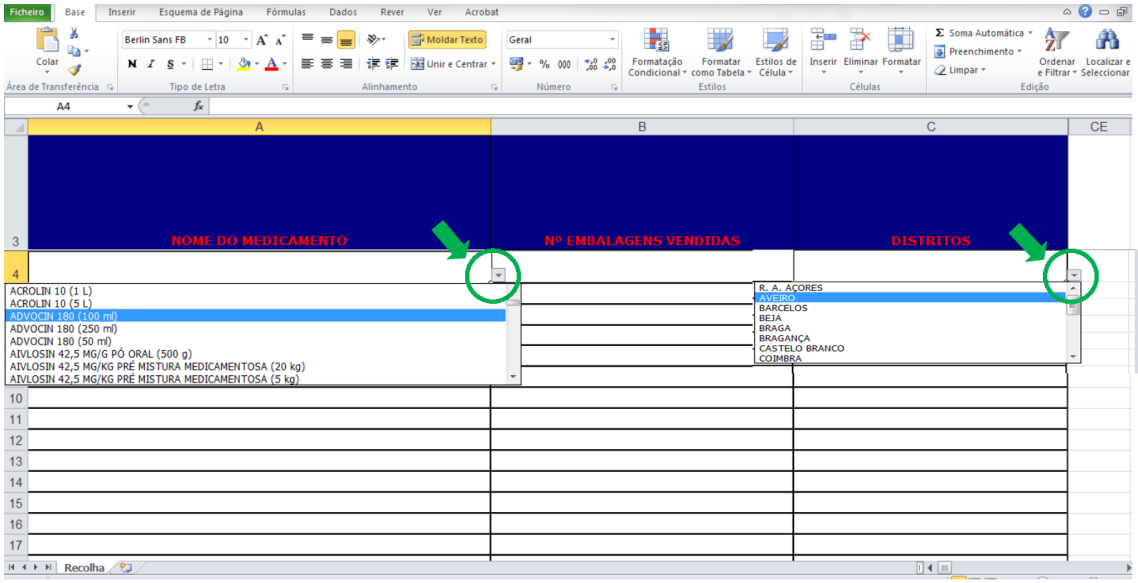


Figure 29 – Excel sheet developed by DGV for harmonized presentation of antimicrobial data by the several MAHs

This was another administrative task verify easy to performed. Nevertheless it was detected a mistake on DGV's file, since one of the VMP commercialized by the client during 2010 was not available at the first column list of possibilities. This problem was communicated to DGV on the e-mail submitting the excel file and sales volume for that VMP was indicated on a single table.

At this moment the report that analysis the collected information is already available for public consultation at DGV's website (47).

The conclusions on antimicrobial consumption trends will then be compared among members states (47).

Personal Experience: Modus Operandi and Principal Handicaps

To accomplish this task I had to request the sales volume to the client, corresponding to those medicines market in Portugal and containing any antimicrobial agent.

After receiving these data, the next step was their introduction on the Excel file. Despite being extremely time-consuming, this task did not raised any issue.

Quality Review Documents and Mock-ups Revision

Sporadically, the client requested the revision of VMP information texts and the implementation of several changes to QRD portuguese versions, in the context of referral procedures or information update.

The revision of mock-ups was also requested and performed accordingly to QRD guidance and portuguese applicable legislation (*Anexo II* of *Decreto-Lei n.º 148/2008, de 29 de Julho*). Figure 30 presents an example of mock-ups revision process, where it is possible to see several comments to be implemented on the original file.

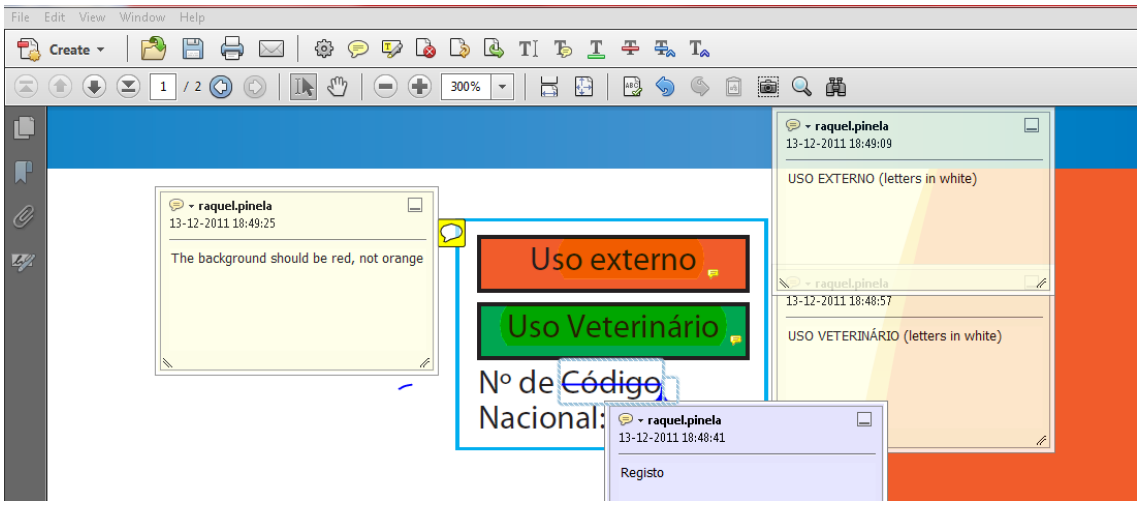


Figure 30 – Example of Veterinary Medical Product's mock-ups revision

Personal Experience: Modus Operandi and Principal Handicaps

Mock-ups revision requires extreme concentration, so that the tiniest detail can be detected. It is also essential to keep in mind the legislation requirements regarding PL and labelling.

This features turn out into long revisions, which can be extremely extending.

In this, context I considered this tasks strenuous and time-consuming. A part from this no other difficulties were felt.

DISCUSSION

This 9 months internship as RA officer was my first contact with employment environment. In the beginning, this was a very intimidating experience, because I could not know, if I was prepared to correspond to company's expectations.

An additional challenging factor of this internship was associated to its field, i.e. RA, which I had now concluded to be more demanding and stressful than other areas, such as the conduction of clinical studies, my current working area. This personal opinion is justified by the highly regulated environment associated to an enormous quantity of procedures, which are not referred in original law and regulation documents, but need to be integrally respected.

The activities developed as a RA officer were focused on post-marketing phase of products lifecycle and encompassed as major tasks and responsibilities human medicines and VMPs MA's management, always in compliance with the applicable legislation. From the analysis of my internship and all activities performed, it is possible to identify several of difficulties of transversal character.

Thus, in general, I felt difficulty to get familiarized with the applicable legislation and requirements of each type of process. There is a lot of information in several documents types, such as: national laws, INFARMED, I.P. press releases, frequently asked questions, among others. The analysis and integration of all this information is an extremely complex and time-consuming process. However, it could not be left unsaid, that the hurdles regarding the adaption to legal framework were only overcome thanks to a strong support from my colleagues, especially from my coordinator Ricardo Andrade, who already has a strong and solid knowledge background. To optimize the knowledge acquired it was essential to put it into practice, trough the realization of all tasks required to conclude a certain regulatory process and achieve regulatory approval. With the continuous practice, trough the development of several similar projects, it was gradually easier to understand the tasks that should be performed and their specific timings and requirements.

Another difficulty felt was related to time management. Sometimes it become particularly demanding to manage a big amount of simultaneous projects and

tasks may start accumulating. Phagecon offers quality scientific-consulting services to pharmaceutical industry, which implies to respect regulatory timelines and to deliver finalised projects on time. However, the workflow of a CRO can be very different from industry, since there are spontaneous requests by clients at any period of the year. In this context, it is not possible to predict future projects and organize them in a temporal manner that better feats working capacities.

Clients' recognition of Phagecon's services and capacity to perform them on time is translated into a lot of new projects, almost every week. As a consequence there may be periods where each collaborator feels overloaded. To ensure that projects are finalised on time, it is essential to be aware of each project importance and urgency, as well as of the possibility to request a deadline extension. This information will allow establishing working priorities and diminishing personal stress. To better face this situation, I had to make an effort to adjust my working rhythm to the high-speed usually practiced at Phagecon and to spend extra working hours whenever necessary to accomplish goals. Time management and tasks prioritization, previously described, were also extremely important to deliver my projects on time.

Despite the difficulties felt, I consider that they were mitigated allowing to positively overcome the internship challenge. The accomplishment of all the objectives initially defined is also proof of internship success, since it allowed to:

- Develop depth knowledge on RA and medicines legal framework and the analytical capacity to understand and predict their impact on usually performed processes.
- Become familiarized with the essential standards and processes that should be followed for obtaining regulatory approvals, and thereby to better understand the specific and realistic aspects of most commonly performed activities.
- Strengthen personal skills such as organization and the capacity to handle several tasks and projects simultaneously and prioritize them, contributing to efficiently manage time and stress.
- Contribute to the success of MMD's projects and Phagecon's goals.

Furthermore I can say that the initially defined goals to this internship were in fact overcome, because I was able to acquire knowledge and MA management experience regarding VMPs, which I initially did not predict or intended.

I also would like to highlight that there were 2 essential factors that contributed to overcome the difficulties previously described and consequently to influence this positive balance of internship as RA officer. Among those factors there is the solid and very complete academic formation acquired during Biomedical Sciences degree and also Pharmaceutical Biomedicine master. The specificity of subjects discussed during the academic years gave me a strong background regarding scientific knowledge and also basic principles of legislative framework.

The second factor was the support from all Phagecon's colleagues, who largely contributed to the success of my internship. Their guidance and support were essential to accomplish projects' goals and to fill in gaps on my knowledge.

In short, I can say that the internship was an extremely important step forward in my professional career because it contributed for the acquisitions and/or development of essential technical and also interpersonal skills. A list of the acquired skills is presented below.

Technical Skills

- General knowledge of human medicines and VMP's legal frameworks.
- Knowledge of CTD structure and basic user of e-CTD.
- Submission of national renewal processes, for both human medicines and VMPs.
- Submission of national variation processes, for both human medicines and VMPs.
- Ability to use INFARMED, I.P. online application regarding type I and type II variations.
- Knowledge of QRD templates and readability requirements.
- Preparation and revision of product information texts.

Interpersonal Skills

- Time management.
- Multitasking and high level of organization.
- Responsibility sense.
- Ability to work under stress and deadlines pressure.
- Increased meticulousness and attention to the smallest details.

CONCLUSION

The experience as a RA officer at Phagecon was extremely rewarding, because it allowed the application, in real situations, of knowledge acquired during Biomedical Sciences degree and Pharmaceutical Biomedicine master. This contact with common RA projects and the opportunity to develop several tasks and activities within those projects, contributed not just for knowledge consolidation, but also for the acquisition of new competences, both technical and interpersonal.

The combination of theoretical knowledge with long term practical training in a real enterprise environment gave me a top higher education and more confidence on my knowledge and working capacities.

These features constitute a great competitive advantage in the current job market, since most of the recent graduates do not have any working experience on their education fields.

This is particularly important in areas with highly structure legislative frameworks, such as RA, whose dominance requires a lot of study but also years of practice. Nevertheless, it is important to have in consideration that being a RA officer requires continuous learning and research. In other words the learning process will never be finished and it will continue to evolve as I gain more professional experience.

REFERENCES

1. Apifarma. O Valor do Medicamento. 2011 [updated 2011; cited 2012 October]; Available from: http://www.apifarma.pt/areas/saudehumana/O%20Medicamento/Paginas/OValordoMedicamento.aspx.

2. Apifarma. A Indústria Farmacêutica em Números 2011.

3. Rägo L, Santoso B. Drug Regulation: History, Present and Future. Drug Benefits and Risks - International Textbook of Clinical Pharmacology. Revised 2nd Edition ed: IOS Press, Uppsala Monitoring Centre; 2008.

4. RAPS. Regulatory Affairs Professional Development Framework - An Overview. 2007.

5. ICH. About ICH - History. 2012 [cited 2012 October]; Available from: http://www.ich.org/about/history.html.

6. ICH. E8 - General Considerations for Clinical Trials. 1997.

7. ICH. The Common Technical Document. 2012 [updated 2012; cited 2012 October]; Available from: http://www.ich.org/products/ctd.html.

8. European Medicines Agency. Product-information templates. 2012 [updated May 2012; cited 2012 October]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000134.jsp&mid=WC0b01ac0580022c59.

9. Chaves J. Grupo - Apresentação. [cited 2012 October]; Available from: http://www.fhc.pt/publico/UserFiles/Downloads/Apresentacao/GrupoApresentacao.pdf.

10. Phagecon - Serviços e Consultoria Farmacêutica L. Manual da Qualidade. 2012.

11. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001on the Community code relating to medicinal products for human use (consolidated version), (2011).

12. INFARMED IP. Extensão ao Procedimento Nacional do Regulamento das Alterações. Circular Informativa No. 200/CD2011.

13. INFARMED IP. Extensão ao Procedimento Nacional do Regulamento das Alterações. Circular Informativa No. 190/CD/8.1.6 2012.

14. European Medicines Agency. Guideline on dossier requirements for Type IA and IB notifications. 2006.

15. Decreto-Lei n.º 176/2006, de 30 de Agosto - Estatuto do Medicamento, (2006).

16. European Medicines Agency. Referral procedures. [cited 2012 June]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0.

17. INFARMED IP. Arbitragens. 2012 [updated 12 October 2012; cited 2012 October]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/AUTORIZACAO_DE_INTRODUCAO_NO_MERCADO/ARBITRAGENS.

18. European Medicines Agency. Q&A: Referral procedures. [cited 2012 June]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000018.jsp&mid=WC0b01ac0580024e97.

19. European Medicines Agency. Annex I - List of the names, pharmaceutical forms, strengths of the medicinal products, routes of administration, marketing authorisation holders in the member states. Assessment report for Nimesulide containing medicinal products for systemic use 2012 [cited 2012 October]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Nimesulide_31/WC500125570.pdf.

20. European Medicines Agency. Annex III - Amendments of the Summary of Product Characteristics and Package Leaflet. Assessment report for Nimesulide containing medicinal products for systemic use 2012 [cited 2012 October]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Nimesulide_31/WC500125572.pdf.

21. INFARMED IP. Perguntas Frequentes - Arbitragens - Gerais. [cited 2012 October]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/PERGUNTAS_FREQUENTES/MEDICAMENTOS_USO_HUMANO/MUH_AIM/ARBITRAGENS_GERAIS.

22. INFARMED IP. Medicamentos de Uso Humano - Lista de Arbitragens concluídas. 2012 [cited 2012 October]; Available from: http://www.infarmed.pt/pt/medicamentos/uso_humano/arbitragens/concluidas.html.

23. INFARMED IP. Submissão Electrónica de Alterações tipo I aos termos da Autorização de Introdução no Mercado (A.I.M.) por procedimento nacional. Circular Informativa No. 079/CA 2005.

24. INFARMED IP. Submissão de Pedidos de Alterações em Formato Electrónico - Manual de Carregamento. [cited 2012 october]; Available from: http://www.infarmed.pt/pt/medicamentos/uso_humano/submissao_alteracoes/manual_subm_alteracoes.pdf.

25. INFARMED IP. Publicação e Actualização dos Resumos das Características do Medicamento (RCM) e de Folhetos Informativos (FI). Circular Informativa No 104/CA 2006.

26. INFARMED IP. Implementação do Acordo Ortográfico na Informação dos Medicamentos. Circular Informativa No. 275/CD 2011.

27. European Medicines Agency. Annex IV - Condition of the marketing authorisations. Assessment report for Nimesulide containing medicinal products for systemic use 2012.

28. European Medicines Agency. Assessment report for Nimesulide containing medicinal products for systemic use. 2012. p. 24-5.

29. INFARMED IP. Perguntas Frequentes - Alterações aos termos de AIM. [cited June 2012]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/PERGUNTAS_FREQUENTES/MEDICAMENTOS_USO_HUMANO/MUH_AIM/GERAIS#11.

30. INFARMED IP. Alterações aos termos de AIM. Circular Informativa No 148/CD 2007.

31. INFARMED IP. Submissão Electrónica de Alterações tipo II de Segurança aos termos da Autorização de Introdução no Mercado (AIM) por procedimento nacional. Circular Informativa No. 095/CD 2009.

32. INFARMED IP. Manual de Submissão Electrónica - Alterações Tipo II de Segurança solicitadas pelo INFARMED, I.P. (AIM de medicamentos nacionais). Versão 2 ed2010.

33. European Medicines Agency. Q&A: Transfer of marketing authorisation. 2007 [updated April 2012; cited September 2012]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000045.jsp&mid=WC0b01ac0580023e80.

34. INFARMED IP. Renovações de Autorização de Introdução no Mercado por Procedimento Nacional – Alteração do procedimento. Circular Informativa No. 195/CD 2010.

35. INFARMED IP. Organização do CD-ROM para Submissão de Pedido de Renovação de AIM por Procedimento Nacional. [cited 2012 October]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/AUTORIZACAO_DE_INTRODUCAO_NO_MERCADO/RENOVACOES_DE_AIM/Legenda.pdf.

36. INFARMED IP. Renovação da Autorização de Introdução no Mercado por Procedimento Nacional - Instruções aos Requerentes. 2010.

37. INFARMED IP. Renovações de AIM – Declarações de Perito Clínico e de Qualidade. Circular Informativa No. 098/CD 2007.

38. INFARMED IP. Perguntas Frequentes (Versão Consolidada) - Renovações de AIM por Procedimento Nacional. 2010.

39. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (Consolidated Version), (2009).

40. Decreto-Lei n.º 148/2008, de 29 de Julho, Diário da República 1.ª série — N.º 145 (2008).

41. Direcção-Geral de Veterinária. Instruções aos requerentes relativas à apresentação dos pedidos referentes a medicamentos veterinários.

42. subgroup T-V. Guideline on the specifications for provision of an electronic submission (e-submission) for a veterinary medicinal product Version 2.1 2011.

43. Decreto-Lei n.º 314/2009, de 28 de Outubro, Diário da República 1.ª série — N.º 209 (2009).

44. 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. Official Journal of theEuropean Union 2010/C 17/01; 2010.

45. Direcção-Geral de Veterinária. Normas referentes às alterações aos termos das autorizações de introdução no mercado por procedimento nacional. [cited 2012 October]; Available from: http://www.dgv.min-agricultura.pt/portal/page/portal/DGV/genericos?generico=17171&cboui=17171.

46. Direcção-Geral de Veterinária. Instruções de Elaboração de Relatórios Periódicos de Segurança. [cited 2012 October]; Available from: http://www.dgv.min-agricultura.pt/portal/page/portal/DGV/genericos?generico=201325&cboui=201325.

47. Direcção-Geral de Veterinária. Relatório Nacional de Monitorização do Consumo de Antimicrobianos - Portugal 2010 2011 [cited 2012 October]. Available from: http://www.dgv.min-agricultura.pt/portal/page/portal/DGV/genericos?generico=2449456&cboui=2449456.