Universidade de Aveiro Secção Autónoma de Ciências da Saúde

2014

MAIRA CHRISTIANE SOCORRO DUARTE ETELVINO

RELATÓRIO DE ESTÁGIO CURRICULAR NA DIREÇÃO DE GESTÃO DO RISCO DE MEDICAMENTOS

CURRICULAR TRAINING REPORT AT RISK MANAGEMENT DIRECTORATE

Universidade de Aveiro Secção Autónoma de Ciências da Saúde
2014

MAIRA CHRISTIANE SOCORRO DUARTE ETELVINO

RELATÓRIO DE ESTÁGIO CURRICULAR NA DIREÇÃO DE GESTÃO DO RISCO DE MEDICAMENTOS

CURRICULAR TRAINING REPORT AT RISK MANAGEMENT DIRECTORATE

Relatório de estágio curricular apresentado à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizado sob a orientação científica da Doutora Maria Teresa Ferreira Herdeiro, Professora Auxiliar Convidada da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro e coorientação da Dra. Maria Alexandra Castro Lopo Morais Bessa Soares Pêgo, Diretora da Direção de Gestão do Risco de Medicamentos, do INFARMED, I.P.

“Todo sucesso oculta uma abdicação” (Simone de Beauvoir)
A meus pais.

o júri

Presidente	Doutor Bruno Miguel Alves Fernandes do Gago, Professor Auxiliar Convidado, Universidade de Aveiro
Vogal- Arguente Principal	Mestre Fernanda Inês de Carvalho Pereira Ribeiro Vaz, Especialista, Faculdade de Medicina da Universidade do Porto
Vogal-orientador	Doutora Maria Teresa Ferreira Herdeiro, Professora Auxiliar Convidada, Universidade de Aveiro

aknowledgments

At first I would like to thank Dra. Alexandra Pêgo for accepting me in DGRM and for always be attentive to my learning process and for the time dedicated to review this report.

I am also indebted to Professor Doctor Teresa Herdeiro who put so much effort in helping me get the chance to have this internship, for all the knowledge transmitted during the academic journey and for the precious help with this report.

I'm grateful to Professor Bruno Gago and Luís Almeida for the constant support and for the always being available to me.

I special thank to all my colleagues of DGRM for teaching me with so much patience and kindness and also for the moments of joy. I would like to thank in particular Dra. Fátima Bragança for the knowledge transmitted and caring.

I'm thankful to my all friends for the good moments and support during my academic journey. I particularly thanks to Kathy Piedade for the always being there for me, Romine Semedo for the honest friendship and kind words and my BBF Annica Barros for listening to my endless drama and for the sincere advices.

I'm deeply grateful to all my family, but specially my uncle Quintino Duarte, my aunt Albertina Duarte, my grandparents and my little cousins for the constant love and support.

I owe a great debt of gratitude to my parents Etelvino and Maria for the unyielding support and for all the sacrifices made since forever and also for the unconditional love. Special thanks to my little brother Ruben who is always supporting and annoying me.

At last, it all resumes by thanking God for all the greatness in my life.

palavras-chave

Farmacovigilância, reação adversa, gestão do risco, segurança do medicamento, notificação de RAM.

resumo

Este relatório é o sumário das atividades realizadas durante 9 meses de estágio na Direção de Gestão do Risco de Medicamentos no âmbito do mestrado em Biomedicina Farmacêutica. O estágio teve o objetivo de complementar os conhecimentos teóricos adquiridos e contemplou as duas principais áreas de ação da Direção: a Monitorização de Segurança de Medicamentos de Uso Humano e a Minimização do Risco.

De entre as atividades da Direção inclui-se a recolha e avaliação de notificações de reações adversas enviadas por profissionais de saúde, utentes e empresas farmacêuticas. As atividades de minimização do risco associado a medicamentos incluem atividades como as alterações de segurança, a gestão dos relatórios periódicos de segurança e dos planos de gestão do risco, a validação das comunicações dirigidas aos profissionais de saúde e a avaliação dos materiais educacionais.

A Direção tem ainda a função de detetar novos sinais de segurança e fazer a sua gestão.

keywords

Pharmacovigilance, adverse reaction, risk management, drug safety, Individual Case Safety Report

abstract

This report is a summary of the activities developed during 9 months of curricular training at the Directorate of Risk Management for Medicines as part of the master degree in Pharmaceutical Medicine. The internship has the purpose of complement the theoretical knowledge previously acquired and was focused on the two areas of the Directorate: Safety Monitoring and Risk Minimization.

The activities of the Directorate include the collection and validation of Individual Case Safety Report received from healthcare professionals, patients and pharmaceutical companies.

The activities of Risk Minimization include the implementation of safety variations, management of periodic safety update report and risk management plan, validation of the direct healthcare professional communication and the evaluation of educational materials.

The Directorate is also responsible to identify and manage safety signals.

Table of contents

Index of Figures

Index of Tables

List of Abbreviations

ACK	Acknowledgment
AR	Adverse Reaction
ATC	Anatomical Therapeutic Chemical
CHMP	Committee for Medicinal Products for Human Use
CIMI	Centre of Information about Medicines and Medical Products
CIOMS	Council for International Organizations of Medical Sciences
CMDh	Coordination Group for Mutual Recognition and Decentralized Procedures
DGRM	Directorate of Risk Management for Medicines
DHPC	Direct Healthcare Professional Communications
DIBD	Development International Birth Date
DIL	Directorate of Inspections and Licensing
EC	European Commission
EM	Educational Materials
EMA	European Medicine Agency
EPITT	European Pharmacovigilance Issue Tracking Tool
EV	EudraVigilance
EVCTM	EudraVigilance Clinical Trial Module
EVDAS	EudraVigilance Data Warehouse and Analysis System
EVPM	EudraVigilance Post-Authorisation Module
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practices
HCP	Health Care Professionals
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IME list	Important Medical Event List
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holders
MedDRA	Medical Dictionary for Regulatory Activities
MS	Member State
NCA	National Competent Authorities
NPS	National Pharmacovigilance System
NUI	Non-Urgent Information
PAES	Post-Authorization Efficacy Studies
PASS	Post-Authorization Safety Studies
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
QPPV	Qualified Person for Pharmacovigilance
RA	Rapid Alert
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SOC	System Organ Classes

SUSAR	Suspected Unexpected Serious Adverse Reactions
UMC	Uppsala Monitoring Centre
WHO	World Health Organization
WWID	Worldwide Unique Case Identification Number
XML	Extensible Mark-up Language

1 Introduction

Medicines undergo extensive studies before marketing approval to ensure safety, efficacy and quality. However because the clinical trials conducted before marketing approval are short term and only involves a restrict population, the safety information obtained is incomplete, and therefore medicines need to be under continuous monitoring to obtain more information about the effects on real conditions (1, 2).

Pharmacovigilance is a science that includes the detection, collection and management of adverse reactions, implementation of measures to minimize risk and communication with the stakeholders and general public. These activities aim to prevent adverse reactions and medicine-related problems and promote the safe and effective use of medicines (1-3).

The pharmacovigilance activities started in the 60' after the great disaster of thalidomide. However, In Portugal regular pharmacovigilance activities only begin in 1992, with the creation of the National Pharmacovigilance System (NPS) with the objective of collect, process and evaluate adverse drug reaction to reduce their burden. INFARMED, I.P. constitute the centre of the NPS and is the coordinator of the pharmacovigilance activities in Portugal (4).

This document is a description of the activities developed during my curricular internship at INFARMED, I.P. in the Directorate of Risk Management for Medicines (DGRM). This internship was performed to obtain the master degree in Pharmaceutical Medicine and to put into practice the knowledge and skills obtained during my academic experience. I will describe in this report, the historic perspective of pharmacovigilance, an overview of the burden of adverse reaction in our society and the current legislation applicable in pharmacovigilance. I will also give an overview of the partners involved in pharmacovigilance, including the host institute INFARMED, I.P. Then I will describe the activities performed at DGRM and the activities that I participated in. To finalize this report I will discuss the difficulties felt during the internship and the accomplishment of my defined learning outcomes.

1.1 Historic perspective of Pharmacovigilance

The concept of the hazard associated with medicines is known for a long time. Since the Hammurabi code (≈ 2200 a.C.) which predicted punishment for the doctor who caused harm to a patient. The Hippocrates Oath (460-370 a.C.) brought the concept of "*primum non nocere"* trying to alert for the harm associated with medical practices and also Paracelsus (1634) gave a very important perspective in the area of medicine hazard when he said that the difference between the positive effect and the poison is the dose (4, 5).

In the following years, the concept of medicine hazard and prevention was kept in mind and some related activities were carried out. For example, the emperor Frederick II demanded for inspections to the medicines used and enforced punishment in case of any harm caused by the potions and elixir used. In the XVII century, the University of Paris demanded for the withdrawal of medicines containing antimony due its toxicity (4, 6).

In 1848 the use of chloroform as anaesthetic concluded in death of many people. Chloroform was introduced in the market a few years before, and was thought to be better than ether due to less adverse reactions. However, the drug caused many deaths due ventricular fibrillation. The safety of the anaesthetic was questioned and was published articles in The Lancet, constituting a primitive form of reporting adverse reactions (7).

In 1906, due the global expansion and economic increase caused by the industrial revolution, the developed countries were facing a massive production of foods and medicines without any hygiene or safety rules. This situation was criticised by Sinclair Lewis who published articles about the negligent production of meat in the Chicago butchers. Therefore in the same year in the United States (US) was approved and published a legislation which forbid the manufacture and sale of adulterated food products or drugs – the Pure Food and Drug Act (4, 8).

In 1937 the commercialization of the Elixir Sulphanilamide caused several deaths in US. Sulphanilamide was already used in powder and tablet form. However the company wanted to produce the medicine in elixir, therefore they mix sulphanilamide with diethylene glycol and tested the flavour, appearance and fragrance with positive results. This new formulation was not tested for safety and was shipped to the entire country. The doctors noticed several deaths in the patients receiving the Elixir and notified American Medical Association who requested the substance for more studies and found that diethylene glycol was a toxic substance. The Food and Drug Administration (FDA) were also notified and started the process for retrieving the drug (9).

To prevent this situation the FDA required that every medicine placed in market should be safe under normal conditions of use, demanding for toxicity studies in the nonclinical phase (4).

The story of modern pharmacovigilance starts with the disaster of thalidomide in 1961-62. Thalidomide was first approved in 1957 in Germany as a safe and effective hypnotic and anti-emetic drug to treat morning sickness and nausea during pregnancy (10). In the following years the drug was approved in Europe, Canada and others countries. The drug was not licensed in US because Frances Kelsey found the data on safety inconclusive and insufficient, and demanded for more nonclinical studies (10, 11).

In Europe a large number of children were born with a severe and rare congenital defect, known as phocomelia. The defect was characterized by the absence of limbs. Phocomelia is a rare defect and was occurring frequently, originating various theories to explain the cause of such abnormality (12).

The association of thalidomide with the congenital defects was found by two different clinicians. The paediatrician Widukind Lenz noticed the increase of births with phocomelia in Germany and did a case-control study verifying that the mothers of the children with phocomelia took thalidomide during pregnancy (12, 13). The results were presented at a paediatric conference(14). In the same year, in Australia, the obstetrician William McBride also noticed the increase of birth with defects and was able to associate it with the use of thalidomide during pregnancy. In the same year he published an article in The Lancet describing the tragedy of thalidomide (12, 15).

However the complete retrieve of Thalidomide from the market was difficult, the drug was withdrawn in Australia and Germany, but because it was commercialized in several countries and under different trade name and the pharmacovigilance tools for collaboration and retrieval from the market were not in place, the drug was still in the market (12). The drug caused more than 10.000 children born phocomelia in 46 countries (10).

The disaster of thalidomide changed the regulatory framework worldwide. The authorities became more rigorous in the approval process, demanded for teratogenicity tests before market and for post-marketing surveillance (10).

In 1962 started the actions to prevent the disaster of thalidomide in the US and was published the 1962 Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, commonly known by the Kefauver-Harris Amendments. This Amendment changed the medicine field in US, giving to the

FDA the power to require for prove of effectiveness and safety of the drug before entering the marketing and demanding for the report of serious adverse reaction (11).

In Europe only is 1965 was created a similar legislation, Council Directive 65/65/EEC of 26 January 1965, which determined that only medicines proved to be safe are approved (16).

The idea of a system for rapid dissemination of safety information was reinforced and led to the creation of World Health Organization (WHO) Pilot Research Project for International Drug Monitoring in 1968 with the purpose of detecting adverse reactions to medicines. In the following years the pharmacovigilance gained life and the Member States started to develop systems to collect and evaluate adverse reactions (17).

The history of pharmacovigilance system in Portugal begins after Portugal joins the Economic European Community in 1986. From then the conditions for the development of pharmacovigilance was being created and in 1991 was published the decree-law nº 72/91 which preview the communication of adverse reactions to drugs and only in 1992 was officially created the NPS (16).

1.2 The burden of adverse reactions and the reports

Adverse reaction (AR) to medicines represents a great burden to society and economy and has a direct impact in the morbidity and mortality (18, 19). In US, the management of AR costs 30.1 billion dollars annually. This cost is mostly due hospitalization, prolongation hospitalization and emergency visits (18). In Europe it is estimated that AR is responsible for around 197.000 deaths per year and costs society 79 billion Euros (20).

Studies have shown AR is the cause of 5-6.5% of the hospital admissions (21, 22) and about 4.3% of the AR leading to hospitalization are preventable (22). Most of the preventable AR is caused by drugs as antiplatelets (including aspirin when used as an antiplatelet), diuretics and Nonsteroidal anti-inflammatory drugs (22). Most of the adverse reactions are type A reaction (AR due the augmented effect of the drug) and drug interactions account for 16.6% of the adverse reactions(21).

Since the implementation of NPS the numbers of AR notified is increasing. The Figure 1 shows the number of adverse reactions reports received in the system since its creation until 2013 (23).

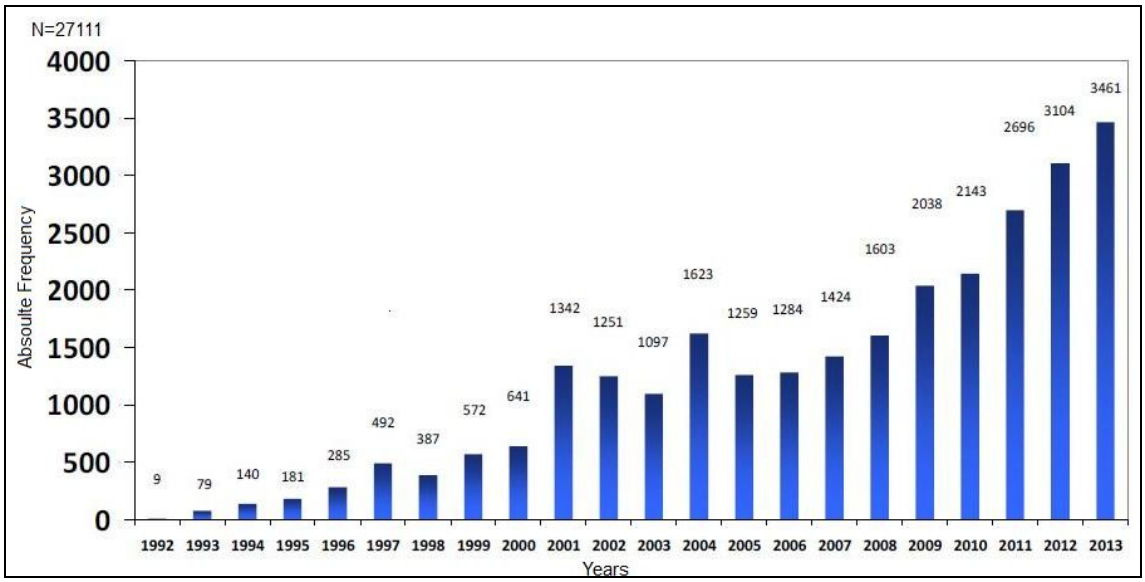

Figure 1: Adverse Reaction reports received in the NPS (Adapted from www.infarmed.pt)(23)

The number of notification per healthcare professional is variable. The Figure 2 shows that until 2005 the physicians were responsible for most of the notifications received in the system. However in the following years the pharmaceutical companies are notifying significantly more, followed in the last years (2009, 2011 and 2012) by the pharmacists. In 2012 the patients became an active part of the pharmacovigilance activities; however the number of notification is low, compared with the other reporters, despite of the increase of the notifications received in 2013 relatively to the previous year (24).

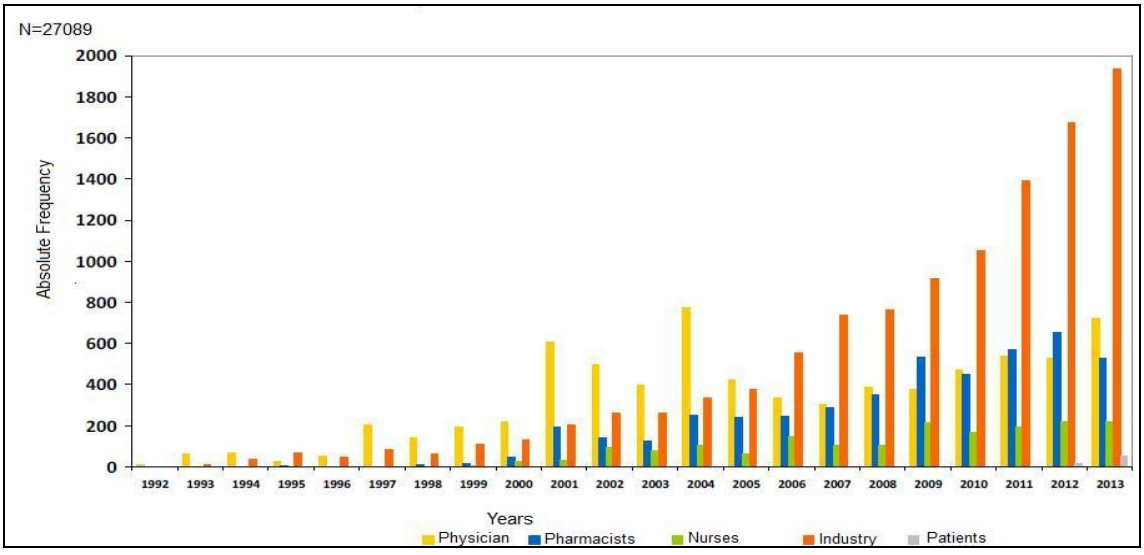

Figure 2: Number of Notifications received by source. (Adapted from Infarmed.pt)(24)

In the last year (2013), was received in the NPS 3461 reports, wherein 1461 were from healthcare professionals, 65 from the patients and 1935 from the pharmaceutical industry. The indirect way (reports by the industry) represents 56% of the reports and the direct way (directly from the healthcare professionals and patients to the system) represents 44%. Concerning the geographic region (Figure 3), the North reported more during the year, followed by Lisbon and Tagus Valley, South, Centre and the islands. Most of the notifications received by the direct way correspond to serious cases, except from the South region which only 20% of the notifications are serious (25).

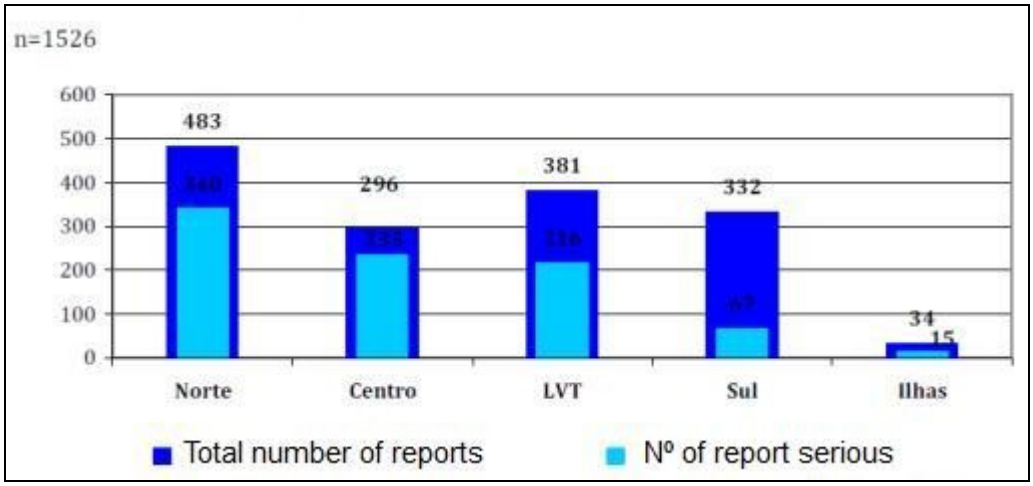

Figure 3: Absolute frequency of reports received by region (Adapted from Infarmed report)(25)

In 2013, the great majority of reports were from the physician, corresponding to 47% of the total, followed by the pharmacists with 35%, the nurses with 14%, the other healthcare professionals with 1%. The patients reported 3% of the reports received which correspond to an increase of 2% from 2012 (25).

From the total of notifications received, after the elimination of duplicates, 3075 correspond to adverse reaction case. Most of the cases received in the system refer to serious adverse reaction cases, which correspond to 78% of the cases. This number is affected by the reports from industry which only reports serious Individual Case Safety Report (ICSR), except from special circumstances of non-serious reports (25).

Considering the classifications of AR cases received by System Organ Classes (SOCs), we can verify the 5 more representatives AR classified by SOC (Figure 4) Most of the AR correspond to general perturbations and alterations in the administration local (25). Considering the cases received according to Anatomical Therapeutic Chemical (ATC) classification of the medicines, we can observe that corresponds to the SOC affected by the drugs. Therefore, we observe that the

vaccines corresponds to the great majority with 12% the same as the Antineoplastic Agents (Figure 5) (25).

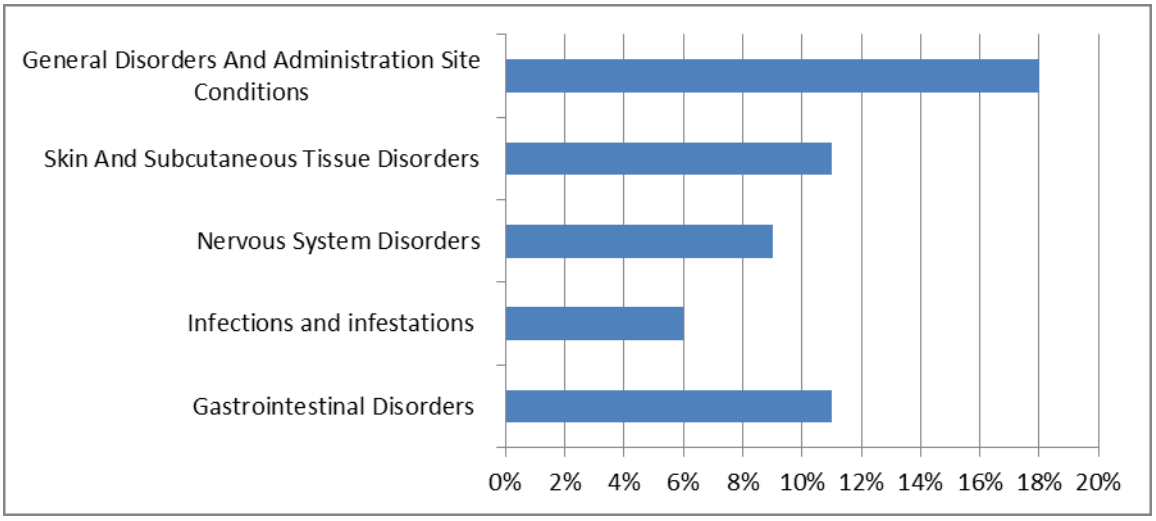

Figure 4: Relative Frequency of the most representative AR cases received in 2013 by SOC(25)

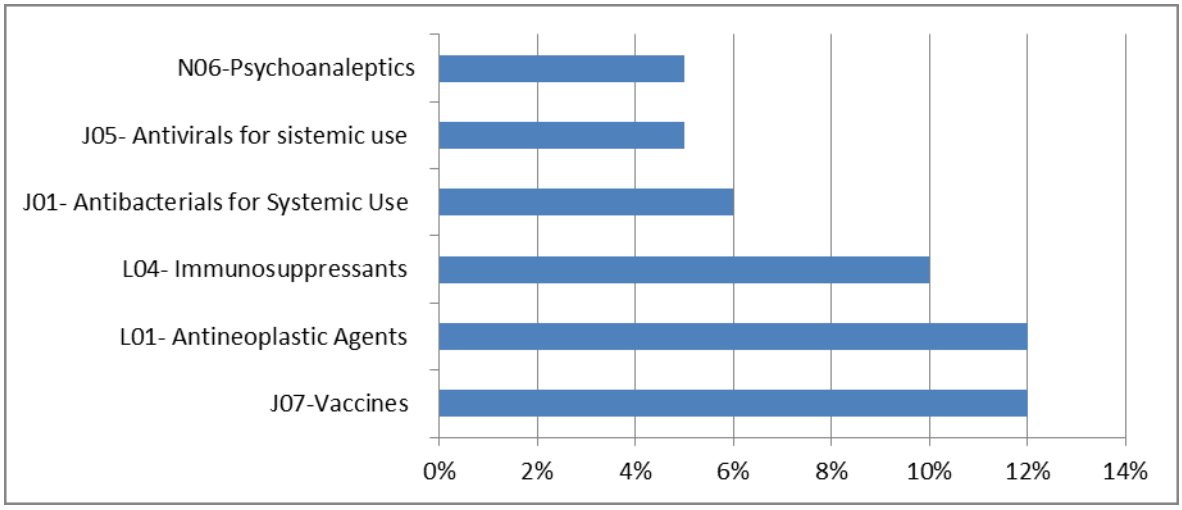

Figure 5: Relative Frequency of the most representative ATC of the AR cases received (25)

The IINFARMED's report for the 1st trimester of 2014 demonstrates a tendency for increase of the total number of notifications. The number of reports received during this period is 1097, which represents an increase of 19% relatively to the same period of the last year. The most representative drugs that caused AR (by ATC) are similar, but the relative frequency is slightly increased. (25, 26)

At the global level, the number of ICSR received in the WHO global Individual Case Safety Report database (VigiBase) is also increasing rapidly in the past 5 years. This year the database reached 9

million ICSR (Figure 6). The developed countries are responsible for the report of the great majority of cases. Around 1,300,000 of the notifications are from patients (27).

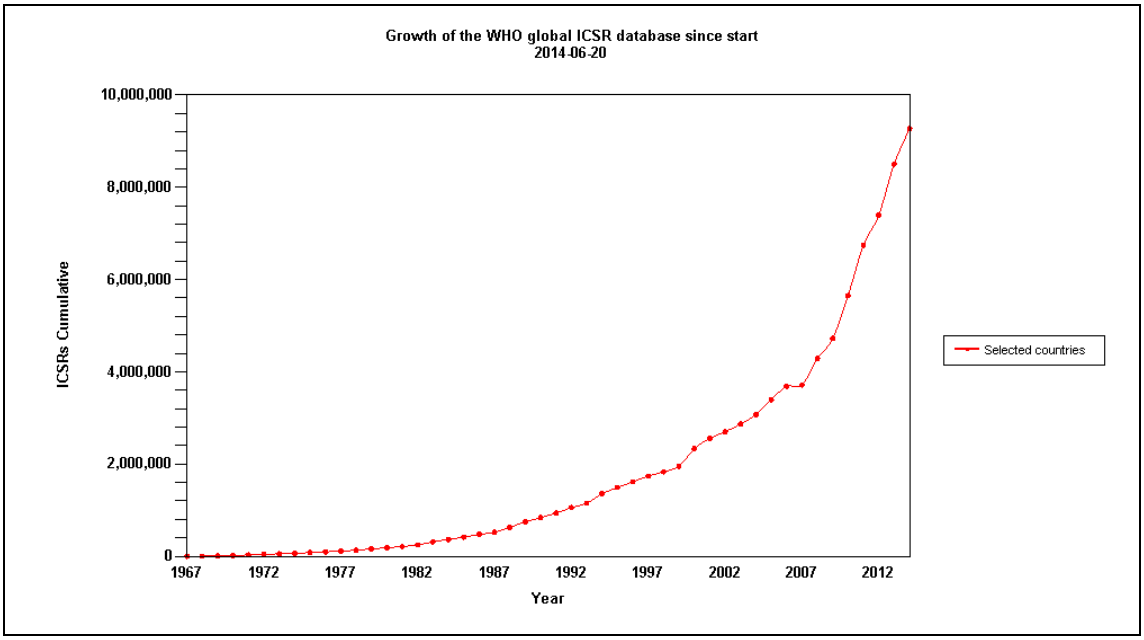

Figure 6: Number of ICSR received in the VigiBase (Adapted from UMC report 66) (27)

1.3 Pharmacovigilance legislation

The pharmacovigilance activities are now regulated by the legislation approved in 2010. This new legislation is in practice since July 2012 and implemented major changes in the pharmacovigilance area. This new legislation aims to rationalize the pharmacovigilance activities and increase patient safety, while increasing the transparency (28). The legislation is applicable to Marketing Authorization Holders (MAH), European Medicine Agency (EMA) National Competent Authorities (NCA).

The applicable legislation in pharmacovigilance includes the:

- Regulation (EU) No 1235/2010 of 15th December;
- Directive 2010/84/EU of 15th December;

This legislation is accompanied by the legally binding act that provides details on the operational aspects - Commission Implementing Regulation (EU) No 520/2012.

The legislation is applicable in 4 different areas: the collection of information, the analysis and understanding of information, the regulatory actions to protect the public health and the communication with stakeholders (29).

With the new legislation, the definition of adverse reaction was enlarged to include the use of medicine outside the terms of marketing authorization, therefore including off-label use, overdose, misuse, medication error, abuse and occupational exposure. Adverse reactions is now defined as any response to a medicinal product which is noxious and unintended (30).

The patients play a direct role in pharmacovigilance by gaining the right to report adverse drug reactions (ADR) directly to the system (30). Another important change is the creation of a new committee in EMA - Pharmacovigilance Risk Assessment Committee (PRAC) responsible for evaluation of safety information and issue recommendations.

The Post-Authorization Safety Studies (PASS) and the Post-Authorization Efficacy Studies (PAES) have now a legal basis and can be requested to monitor the benefit-risk balance of medicinal products (29). The PASS has a new definition, format and protocol and must be approved by the PRAC. PASS is therefore defined as a study conducted with an authorized medicine to assess, identify and characterize the safety hazard, confirm the safety profile or measure the effectiveness of risk minimization measures (30).

The legislation required the MAH to maintain a pharmacovigilance system master file (PSMF) for submission or inspection by the authorities. The document must contain the safety information of the medicinal product. Along with the PSMF the MAH must indicate the qualified person for pharmacovigilance (QPPV) who is continuously responsible for the pharmacovigilance. The QPPV must be qualified and trained to execute pharmacovigilance activities, reside in EU and be contactable.

This legislation introduced the concept of additional monitoring. The medicines under additional monitoring have a black inverted triangle in the package leaflet (PL) and in the summary of product characteristics (SmPC). This black triangle indicates that the medicine is being monitored more closely than the others, usually because there is less information available. The additional monitoring applies to biologics, medicine derived from plasma, medicines approved after 2011 and medicines approved under exceptional circumstances (31). This black triangle has the purpose of increase the transparency with the healthcare professionals and consumers.

The Periodic Safety Update Report (PSUR) has an approach more proportionate to the risk of the medicine. Therefore medical products considered with lower risk, as generics, homeopathic drugs, traditional herbal and well-established use medicinal product are exempted from submit the PSUR. The PSUR is more focused on discuss the benefit-risk profile than only the risks. The

dates from PSUR submission are more harmonized and are specified in the EMA's European Union Reference Date list (32).

The Risk Management Plan (RMP) became mandatory for all the marketing authorization process and should describe in detail the risk management system. The structure of the RMP is new, is composed by 7 parts, divided into modules. To increase the transparence and to inform the public about relevant safety information about medicines, the summaries of the RMP are now available to public. EMA issued the first RMP summary to public concerning a newly authorized medicine. The summary describes the safety information known and unknown and the measures taken to prevent or minimize the risks. During 2014, EMA will publish the summaries for all the newly centrally authorized medicines and in a posterior phase will be published the summaries of the previously authorized medicines (33).

To support the new legislation of pharmacovigilance was developed a set of guidance which replaces the Volume 9A of the Rules Governing Medicinal Products in the EU - the Guidelines on Good Pharmacovigilance Practices (GVP). The GVP applies to all medicines approved in EU and applies to MAH, NCA and EMA. The GVP is constituted by 16 modules, each one covering a major pharmacovigilance processes (28).

The GVP has the following modules:

- Module I – Pharmacovigilance systems and their quality systems
- Module II – Pharmacovigilance system master file
- Module III – Pharmacovigilance inspections
- Module IV – Pharmacovigilance audits
- Module V – Risk management systems
- Module VI – Management and reporting of adverse reactions to medicinal products
- Modules VII – Periodic safety update report
- Module VIII – Post-authorisation safety studies
- Module VIII addendum I – Member States' requirements for transmission of information on non-interventional post-authorisation safety studies
- Module IX – Signal management
- Module X – Additional monitoring
- Module XI – Public participation in pharmacovigilance (Not released yet)

- Module XII –Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication (Not released yet)
- Module XIV – International cooperation (Not released yet)
- Module XV – Safety communication
- Module XVI – Risk minimisation measures - Selection of tools and effectiveness indicators.

The pharmacovigilance regulation is applicable in all member states (MS). However the Directive must be transposed to the national legislation. In Portugal the Directive was transposed into the Decree-Law 20/2013 of 14 February 2013.

In October 2012, the new legislation was amended to increase patient protection by allowing prompt notification and assessment of safety issues. Therefore, was created the regulation N 1027/2012 and the Directive 2012/26/EU, applicable since 2013.

The Directive 2012/26/EU was transposed into the national legislation by the Decree-law 128/2013 of 5 September 2013, amending the previous Decree-law (34).

The Directive 2011/62/EU of 8th June 2011 amends the Directive 2001/83/EC with regard of the falsified medicines. The Directive aims to prevent the introduction of falsified medicinal products into the legal chain (35) .

2 Internship Objectives

My objectives for this curricular internship are:

General outcomes:

- Gain professional experience in the pharmacovigilance field.
- Consolidate the knowledge acquired during my academic experience.

Specific outcomes:

- Understand the pharmacovigilance procedures through the Competent Authority point of view.
- Comprehend the pharmacovigilance legislation and GVP in practical context.
- Understand the connection between the Agency and National Competent Authorities.
- Be autonomous and efficient in processing, analysis and validation of ICSRs.
- Understand the structure of the PSUR and RMP and their importance in the pharmacovigilance.
- Comprehend the importance and be able to validate tools to minimize the risk associated to medicines.
- Increase my skills to manage time and work.
- Increase my skill of communication, critical sense and teamwork.

3 Host entity – Autoridade Nacional do Medicamento e Produtos de Saúde, I. P

INFARMED - *Autoridade Nacional do Medicamento e Produtos de Saúde, I. P*. (National Authority of Medicines and Health Products, I.P.) is a public institute under the aegis of the Ministry of Health, with administrative and financial autonomy and with its own patrimony. Infarmed is responsible to regulate and supervise medicines of human use, medical devices, cosmetics and products for personal hygiene, according with the most elevated standards. The main goal is to protect public health and assure the healthcare professionals and patients have access to medicines, medical devices, cosmetics and products for personal hygiene safe, effective and with quality. (36)

The attributions of Infarmed are (36):

- Contribute to definition and execution of health politics of human medicines, medical devices, cosmetics and products for personal hygiene.
- Regulate, evaluate, authorize, supervise, assure surveillance and control of the investigation, production, distribution, commercialization and use of medicines, medical devices, cosmetics and products for personal hygiene.
- Ensure the compliance with the standards applicable to authorization of clinical trials and monitor the compliance with the good clinical practices.
- Ensure the quality, safety, efficacy and cost-effectiveness of medicines for human use, medical devices, cosmetics and personal hygiene products.
- Monitor the consume and use of medicines.
- Promote the access to information necessary for the rational use of medicines, medical devices, cosmetics and products for personal hygiene.
- Promote and support investigation related to science, pharmaceutical technology, biotechnology, pharmacology, pharmacoeconomy and pharmacoepidemiology.
- Ensure the participation and integration in the European network related with the evaluation, supervision of human medicines, including the articulation with the European Medicine Agency, European Commission (EC) other European institutions
- Assure the adequate integration and participation in the ambit of the network of medicines for human use and health products of EU and the network of official laboratories of quality evidence of medicines of Europe.

- Ensure the international obligation of Portugal particularly within the European Union and within the European Council especially in the European Pharmacopoeia Commission and in United Nations, in the area of control of narcotics and psychotropics.
- Develop activities of national and international cooperation.

Infarmed assures the representation and participation of Portugal in the European System of Medicines in the activities of evaluation and supervision in the committees of EMA, EC and the European Network of Medicines and Health Products Authorities. Infarmed activities articulates with EU using Telematics Network, these activities include the system of alert and rapid exchange of information on quality and safety, the EudraVigilance and the management of mutual recognition procedures for medicines authorisation, clinical trials and EuroPHARM (database for medicinal products authorised in the EU). Infarmed articulates with WHO medicines monitoring system through the Uppsala Monitoring Centre. The institute also cooperate with Portuguese speaking countries like Brazil, Cape Verde, Mozambique and Angola and Macao (37).

The organization of the institute is represented in the organogram:

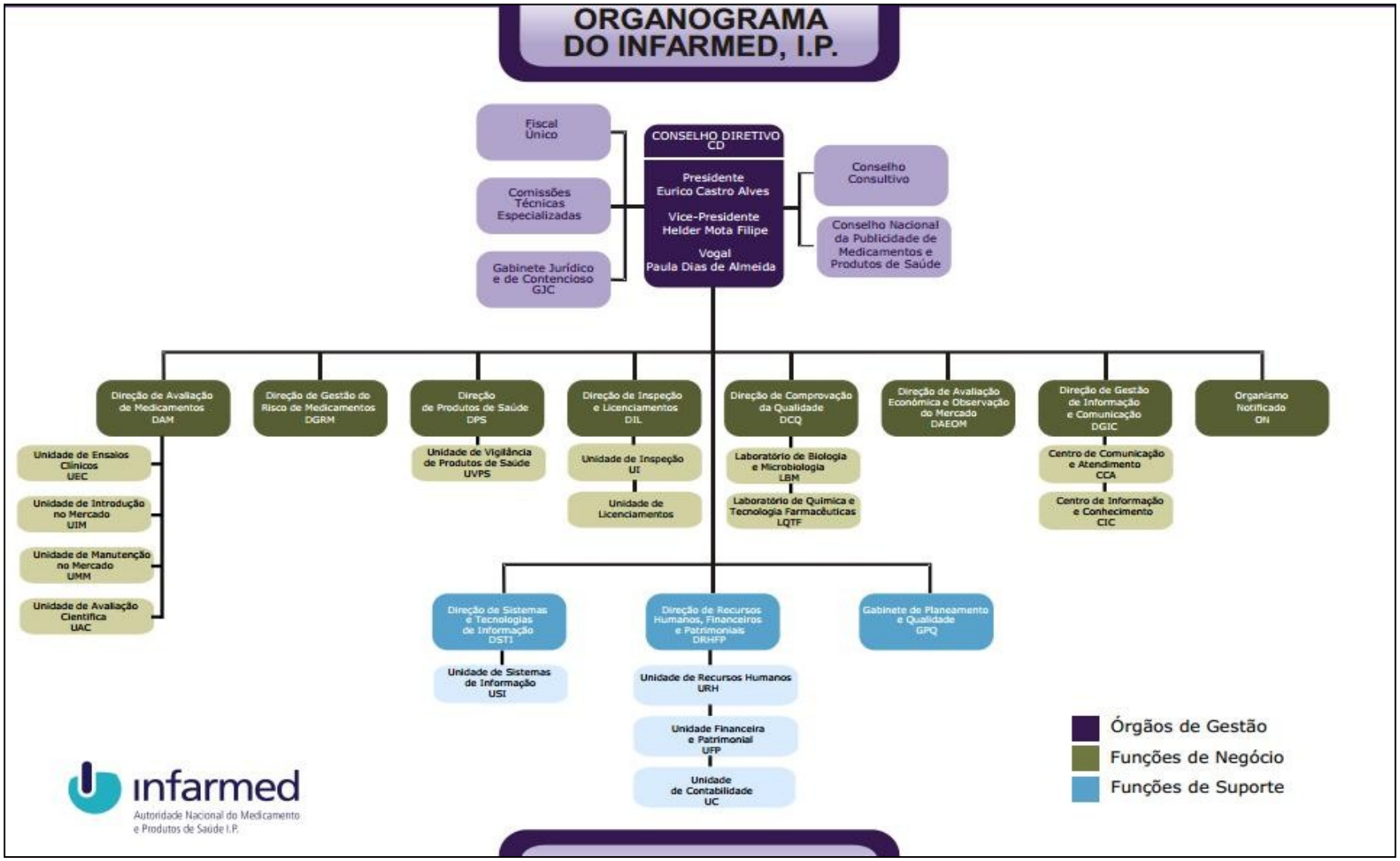

Figure 7: Organogram of INFARMED, I.P.

3.1 Directorate of the Risk Management of Medicines

DGRM is the directorate responsible for the pharmacovigilance activities. The mission of DGRM is to guard and protect public health by managing the risk associated with the medicine authorized in the Portuguese market. DGRM works to identify and evaluate medicines risks, implement measures to minimize risk and communicate with healthcare professionals, patients and general public. And it is also responsible for the coordination of National Pharmacovigilance System (38).

The functions of DGRM are (39, 40):

- Manage the pharmacovigilance alert system of EU and ensure the participation in the monitoring program of WHO.
- Ensure the monitoring of medicine safety by monitoring the PSUR and the RMP.
- Promote epidemiologic studies and collaborate with international institutes on epidemiologic studies.
- Collaborate with the medicine committee in terms of pharmacovigilance.
- Implement safety measures and elaborate benefit-risk reports.
- Represent Infarmed on pharmacovigilance responsibilities.

DGRM works in the collection, evaluation and communication of AR to drugs and elaborate causality assessment for the reports received. The Directorate assures that the safety concerns with medicines are promptly identified and resolved (40).

The DRGM is divided in three working groups, the safety monitoring, risk minimisation and the signal management. The safety monitoring is responsible for the collection and analysis of adverse reaction reports received from MAH, healthcare professionals and patients. The risk minimization team is responsible for the implementation of safety measures. The signal management team is responsible to perform the identification and management of safety signals.

3.2 The Quality system

The Infarmed quality system is based on the norm NP EN ISO 9001: 2008. Quality is a responsibility shared between all the collaborators along with the quality manager. The Quality System of Infarmed aims to satisfy the stakeholders while continuously improve (41).

The Quality Management System is composed by a Quality Manual, Process Record, General Procedures, Quality and Operations procedures and the Working instructions and Models (41).

The certified procedures of Infarmed are audited periodically and the system is revised every year (41). DGRM has two certified procedures, one concerning the safety monitoring of medicines for human use, including the signal management and the other related with the implementation of risk minimization measures (41).

4 National Pharmacovigilance System

In 1991 the Decree-law 72/91 which transposes the European Directive, states that the MAH and the healthcare professionals should notify to *Direção-Geral de Assuntos Farmacêuticos* (DGAF) the adverse reactions to medicines that they became aware (4).

Only in 1992 the legislative order 107/92 officially created the NPS with the objective of study and analyse adverse reactions to medicine. Later in 1993 was created the National Institute of Pharmacy and Medicine (INFARMED) and in consequence the DGAF was extinct (4).

However, the healthcare professionals' reports were very low maybe because of the unawareness of the system or lack of motivation, this fact conducted to the decentralization of the system which permitted a better divulgation and allowed the healthcare professionals to be more included and motivated to report (16).

In 2000 the system was decentralized with the creation of 4 regional centres in partnership with universities: North, Centre, South and Azores (extinct). These centres aimed to promote the pharmacovigilance activities, involving the universities, and being more closely to the healthcare professionals. In 2003, the system was re-organized and the unit of south was restricted to the south region and was included the regional centre of Lisbon and Tagus Valley (4). The pharmacovigilance units have technical and administrative autonomy and are responsible for the reception, classification, processing and validation of ICSR and to elaborate the causality assessment report for the ICSR. The Units are also responsible for promoting the system and the spontaneous report in their geographic region (16)

Infarmed is responsible for coordinate and audit the system periodically. Infarmed is also responsible to promote the notification of adverse drug reaction by the healthcare professionals and patients; create and promote electronic means to facilitate the notifications; publish in the website institutional information concerning the safety of medicines (42).

The healthcare professionals are responsible to communicate to Infarmed or the regional centres, as soon as possible, adverse reactions, suspected serious adverse reaction and the unexpected adverse reactions that they become aware (42). The MAH should report to DGRM all the serious adverse reactions cases occurred in Portugal, reported from patients or healthcare professionals (or from literature). The patients can report serious and non-serious adverse drug reactions to MAH, regional units or directly to DGRM.

The intervenient of the system and their interaction are represented in Figure 8. The MAH reports to DGRM all serious ICSR they became aware. DGRM is responsible to report all serious cases to EudraVigilance and periodically to VigiBase. DGRM is also responsible to send the cases received directly from HCP and patients to the respective MAH (DGRM sends the serious and non-serious cases).

Once EudraVigilance database is completely functional the MAH will be responsible for reporting all serious ICSR occurred within and outside EU directly to EudraVigilance and the MAH will also report the non-serious ICSR occurred in EU to EudraVigilance. Competent Authorities (including Infarmed) will submit to EudraVigilance all the serious and non-serious ICSR reported to them, occurred in the national territory.

The national Pharmacovigilance System is therefore composed by the DRGM, the 4 Regional Unit of Pharmacovigilance (4), the MAH, healthcare professionals and more recently the patients.

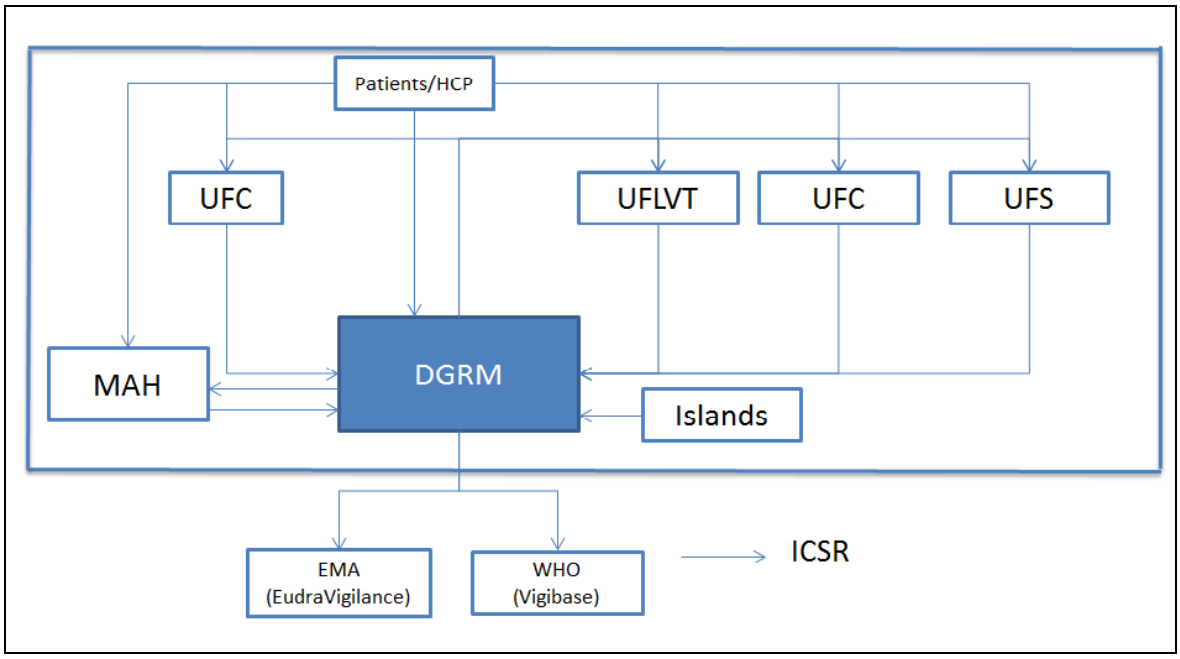

Figure 8: The interaction between the intervenient within the NPS and with EMA and WHO

The NPS is responsible for the activities related to monitoring and preventing adverse reactions to medicines (42):

- Systematic collection of the information related with the risk of medicines for patients and public health, especially in what regards to ADRs.
- Evaluation of the information related to the risks associated with medicines.
- Implementation of measures to minimize the risk associated with the use of medicines.

- Adoption of necessary regulatory measures related to marketing authorization.
- Handling and processing of the safety information following the national and the European regulation and communicating with the member states.
- Communication of safety information with the healthcare professionals and the public.

5 Entities involved in Pharmacovigilance activities

The pharmacovigilance activities involve various partners to facilitate the exchange of information about adverse drug reaction (ADR) and to permit rapid actions to minimize the risks and prevent adverse reactions. In this chapter I will describe the international entities involved in Pharmacovigilance that articulates with Infarmed specially EMA and the committees and the database for collection of reports.

5.1 European Medicines Agency

European Medicines Agency (EMA) is a decentralized agency created in 1995, responsible for the scientific evaluation of medicines for use in the European Union (43). The main goal of the Agency is to promote public and animal health by supervising and evaluating medicines for animal and human use (44).

The general functions of the Agency are (45):

- Provide recommendations on the quality, safety and efficacy of medicines, and others issues relevant to public and animal health that involve medicines in accordance with the EU legislation.
- Evaluate procedures to help bring new medicines to the market by means of a single, EU-wide marketing authorisation granted by the EC.
- Implement measures for continuously supervising the quality, safety and efficacy of authorised medicines to ensure that their benefits outweigh their risks.
- Stimulate the development of new and innovative medicines and provide scientific advice in the development process.
- Recommend safe limits for residues of veterinary medicines used in food-producing animals.
- Work with the patients, healthcare professionals and other stakeholders to solve commons issues.
- Publish impartial and comprehensible information about medicines and their use (45).

EMA works throughout the entire process of the development, market approval and post-marketing surveillance of the medicines and is responsible for the scientific evaluation of applications for marketing authorization for medicines in the centralised procedure.

The post marketing activities include pharmacovigilance activities, to constantly monitor the safety of medicines and take actions in case of alterations in the benefit-risk balance of a medicine.

The pharmacovigilance activities taken by the Agency are (44):

- Provide support on pharmacovigilance activities for medicines authorized though centralized procedure;
- Develop guidelines and setting standards;
- Coordinate the monitoring of pharmaceutical companies' compliance with pharmacovigilance obligation;
- Inform the public about the safety of medicines and contribute to international cooperation activities with authorities outside EU.

The Agency is also involved in referrals procedures to resolve issues concerning safety or benefit-risk balance of a medicine. EMA is responsible for coordinate inspection in connection with the assessment of marketing-authorisation applications or referrals. The inspections may cover the good manufacturing practice, good clinical practice, good laboratory practice or pharmacovigilance (44).

5.1.1 Pharmacovigilance Risk Assessment Committee

The Pharmacovigilance Risk Assessment Committee (PRAC) is the committee responsible for the assessment and monitoring human medicines safety created with the new legislation and active since July 2012 (44). The committee is constituted by a chair and a vice-chair, one member and an alternate nominate from each MS, one member and an alternate nominated by Iceland and by Norway, six independent scientific experts nominated by the European Commission, one member and an alternate to represent the healthcare professionals and one member and one alternate representing the patients organizations (46).

PRAC is responsible for all the activities related to risk management, including the activities of detection, assessment, minimization and communication of adverse reaction. PRAC is responsible for design and evaluation of post-authorization safety studies, for emit recommendation on risk management systems, urgent Union procedures due safety reasons, periodic safety update reports single assessment, signals detection, and for pharmacovigilance audits, PRAC is also involved in the establishment and updating the list of EU Reference Dates, and the list of medicinal products requiring additional monitoring. PRAC is involved in the process for renewals,

annual re-assessments and safety type II variations of centralized medicines. For decentralized medicines PRAC emits an opinion on the risk management plans/systems, renewals, safety type II variations, at the request of a Member State. PRAC activities include the functionalities of the EudraVigilance database and the PSUR repository, the choice of the black symbol to identify medicines for additional monitoring and literature ADR monitoring (47, 48).

The PRAC recommendations are directed to the Committee for Medicinal Products for Human Use (CHMP) when concerning the safety of centralized medicines and referral procedures or to Coordination Group for Mutual Recognition and Decentralized Procedures – human (CMDh) concerning medicines used Member States approved by mutual recognition or decentralized procedures (46).

5.1.2 EudraVigilance

EudraVigilance (EV) is a database launched by EMA in 2001 for transmission, recording and managing electronic adverse events reports. The database was created to support signal identification activities in EU, including EU rapid-alert and incident-management system for response to new safety data. The database permits the scientific assessment of safety data carried out by the regulatory authorities and permit the pharmaceutical companies to have access to the entire safety data available about their medicines (49, 50).

The database includes an automated safety and message processing mechanism using XML-based messaging and a large reference pharmacovigilance database incorporating an extensive query and tracking and tracing capability, following the ICH specifications (50). EV contains information concerning suspected unexpected serious adverse reactions (SUSARs) reported by sponsors which are collected and managed in the EudraVigilance Clinical Trial Module (EVCTM) and the adverse reaction reports collected by national regulatory authorities and pharmaceutical companies which are saved in the EudraVigilance Post-Authorisation Module (EVPM).

The system is supported by the EudraVigilance Gateway, a data-processing network for the secure exchange of adverse reaction data and the EudraVigilance Medicinal Product Dictionary (EVMPD), implemented to allow for the coding of medicinal product information as reported in ICSRs. The analysis and signal detection activities are supported by the EudraVigilance Data Warehouse and Analysis System (EVDAS) (51).

5.1.3 Committee for Medicinal Products for Human Use

The Committee for Medicinal Products for Human Use (CHMP) is the committee at the European Medicines Agency that is responsible for preparing opinions on questions concerning medicines for human use (52).

CHMP is responsible for conduct initial assessment for marketing approval procedures for centralized medicines and CHMP is also responsible for post authorization activities about these medicines. The CHMP is involved on mutual-recognition and decentralized procedures by arbitrating in case of disagreement (53).

CHMP activities also includes the provision of assistance to companies researching and developing new medicines, the preparation of scientific and regulatory guidelines for the pharmaceuticals industry and cooperation with international partners on the harmonisation of regulatory requirements for medicines (53).

CHMP is responsible for publishing the summary of Summary of Product Characteristics (SmPC), labelling and package leaflet (patient/user information leaflet) for centralized medicine, and details of the procedural steps taken during the assessment process (53).

5.2 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICH is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use created with the purpose of increasing the harmonization of technical requirements between EU, Japan and US, in order to develop and register medicinal products with high quality, safety and efficacy in a cost-effective manner (54).

The initiative was launched in 1990 and brings together the drug regulatory authorities and the pharmaceutical industry from the three ICH regions to discuss and establish common guidelines, therefore simplifying the regulatory framework and reducing duplicate work (55).

The activities of ICH have resulted in several guidelines, divided into four categories (Quality, Safety, Efficacy and Multidisciplinary) a standardized and highly specific dictionary of medical terminology to codify adverse reaction (MedDRA), facilitating the sharing of information internationally and signal detection and in the development of the Common Technical Document (CTD) which is a document to simplify the marketing authorization application (56).

5.3 Council for International Organizations of Medical Sciences

Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established by WHO and United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949.

The membership of CIOMS includes 49 international, national and associate member organizations, representing many of the biomedical disciplines, national academies of sciences and medical research councils. CIOMS was created to facilitate and promote international activities in the field of biomedical sciences, to maintain collaborative relations with the United Nations and to serve the scientific interests of the international biomedical community in general (57).

CIOMS have several working group in the area of drug development and medicines use. The working groups emit recommendations about adverse reaction reporting (including the introduction of a standardized reporting form), reporting of periodic drug safety updates, core clinical safety information about medicines, evaluation of benefit/risk balance, current challenges of pharmacovigilance, management of safety information from clinical trials and development safety update report and signal detection in pharmacovigilance (58).

5.4 World Health Organization

WHO is the directing and coordinating authority for health within the United Nations system, which plays an important role in pharmacovigilance. WHO is responsible for international drug monitoring program - the Uppsala Monitoring Centre (UMC). The activities developed by the monitoring program includes the identification and analysis of new AR signals from the ICSR submitted by the national authorities members, exchange of information between WHO, UMC and the national centres, publications of periodical newsletters, guidelines and pharmacovigilance books (59).

UMC developed and maintains the VigiBase – a global database to keep record of ICSR sent by national authorities. VigiBase is the largest and most comprehensive database of adverse reaction. The main purpose of VigiBase is to provide the evidence from which potential medicine safety hazards may be detected (60).

6 On the job training

6.1 Initial training

In the first two weeks at DGRM I had an initial training with the collaborators of DGRM. The training purpose was mostly to introduce me to the activities of DGRM and give me insights of pharmacovigilance and risk management. The training included the following topics:

Presentation of DGRM and its functions and the articulation with EMA, European Commission and WHO. The training also included the functions of EMA. This initial training was given by the director of DGRM.

Quality Management System of Infarmed was explained by the quality manager. The training included an explanation about the processes and procedures of DGRM and the importance of consulting the processes, work instructions and models applicable to each activity. It was also explained the concept of nonconformity which is originated when the quality process is not complied. Nonconformities should be registered and justified.

ADR reception from healthcare professionals and patients and the Portal RAM: in this topic I learned about the concepts of NPS, CIOMS, ICH, causality assessment and differences between the reports received from MAH and patients. I learned about the Portal RAM, a website created to permit online reporting from healthcare professionals and patients.

SVIG and EudraVigilance are two important tools to receive and transmit ICSR (using XML file). National Database of Pharmacovigilance (SVIG) is the database for AR cases of Infarmed and it contains all cases received by the healthcare professionals, patients and MAH. EudraVigilance is the European database which contains cases received from NCA from Europe.

Reception and analysis of ADR from MAH: I learned about how MAH and DRGM exchange ICSR.

Signal Management and ADR search: I learned about the process of identifying possible risks and search for possible signals.

PSUR and Worksharing: This topic was to explain about the PSUR format and the European worksharing to facilitate and reduce duplication of work in the evaluation of PSUR.

Educational Materials: The educational materials aim to elucidate the healthcare professionals and patients about the risks associated to a medicine and how risks can be prevented or

mitigated. In the training about educational materials I learned how the educational materials are evaluated at DGRM.

Direct Healthcare Professional Communication, informative circulars, PRAC, Non-Urgent Information/Rapid Alert and European Pharmacovigilance Issue Tracking Tool (**EPITT)**: I learned about how these communications are made and how it's published in the Infarmed's website. It was explained the important tools to identity important risks concerning marketed medicines in EU.

6.2 Safety monitoring

An adverse reaction is a response to a medicinal product which is noxious and unintended and has a reasonable possibility of causal relationship between the drug and the event. Adverse reactions definition includes the use of medicine in the marketing authorization terms, but also overdose, off-label use, misuse, abuse, medication errors and occupational use (61).

- **Overdose:** when the medicine is administered above the maximum dose recommend in the product authorised information (61).
- **Off-label use:** when the medicine is used intentionally with a different medical purpose from the described in the authorised product information (61).
- **Misuse:** when the medicine is intentionally and inappropriately used not in accordance with authorised product information (61).
- **Medication error:** any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or consumer(61).
- **Abuse:** when a medicine is used sporadic or persistently in an intentional excessive dose with harmful physical or psychological effects (61).
- **Occupational exposure:** refers to the exposure to a medicinal product in the professional or non-professional occupation (61).

The adverse reaction definition implies a minimum of causality association with the drug, the contrary of an adverse event. However, for regulatory reporting purposes all spontaneous reports notified by healthcare professionals or patients is considered an adverse reaction since the primary source has suspected of a causal relationship, unless the contrary is specifically stated. The person who reports the adverse reaction is considered the primary source either is a healthcare professional or a patient or consumer (61).

AR can be classified as serious or non-serious. Serious adverse reaction corresponds to an AR that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly/birth defect. Adverse event which may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences are considered serious. To facilitate the classification of adverse events was created an important medical event (IME) terms list, in which are listed the adverse events considered serious (61).

An Individual Case Safety Report (ICSR) valid for reporting should include the four minimum criteria:

- At least one identifiable reporter;
- One single identifiable patient;
- At least one suspect adverse reaction;
- At least one suspect medicinal product.

The primary source can be characterized by qualification, name, initials or address, the contacts details should be recorded for follow-up activities whenever possible. However if the reporter doesn't wish to provide contacts details the case is still valid. The patient should be identified by the initials, date of birth, age, age group or gender. The suspect adverse reaction should be described using the terms in the MedDRA to facilitate understanding and signal detection (61).

In case of lack of any of these information, the case is not valid for report and the receiver should make efforts to obtain the missing data, if it is not possible to complete the case it does not qualify for reporting, but can be saved in the database (61).

Adverse reaction cases should be as complete as possible, particularly those concerning pregnancy, death of the patient or reports containing new risks or changes in the known to permit the scientific evaluation (61).

Special situations reports:

Pregnancy: in case of exposure of the embryo or foetus to the medicinal product should be made efforts to obtain information on the outcome and development of the child. These reports should be more complete as possible to assess the causal relationship. Cases with abnormal outcomes for example congenital anomalies, problems in development or foetus death should be considered serious and reported within 15 days. Cases with normal outcome or induced

termination of pregnancy should not be reported, however should be collected and discussed in PSURs. In case of medicines which are contraindicated in pregnancy should be followed an expedited reporting (61).

Breastfeeding: Suspected AR which occurs in infants following exposure to a medicinal product from breast milk should be reported (61).

Use in paediatric or elderly population: the safety information about the medicine use in paediatric and elderly should be recorded, once this population is not included in clinical trials, and there's lack of information. Therefore the cases reported should contain the age or age group to identify potential signals (61).

Reports of overdose, abuse, off-label use, misuse, medication errors or occupational exposure: in case of no adverse report associated with these situations should not be reported as ICSRs, however they should be considered in the PSUR as applicable. In case of adverse event associated should be reported according to the seriousness criteria. The terms overdose, abuse, off-label use, misuse, medication errors or occupational exposure should be reported using the closest MedDRA terms available (61).

Lack of therapeutic efficacy: these ICSR does not qualify for reporting unless in situations where the medicines is used in critical conditions or in life-threatening diseases, vaccines and contraceptives where should be reported in 15 days (61).

The special cases when the medicine is used in pregnancy or during breastfeeding, the ICSR should be elaborated according with the indications on GVP VI accordingly with the criteria described:

- If the foetus or infant experiences adverse reaction due to drug exposure in uterus or from breast-milk should be created a case to the child/foetus and the information relatively to the parent is filled in the section concerning the parent.
- If the parent and the child/foetus experience adverse reaction should be created two separated ICSR and they should be identified as related cases.
- If the parent experience adverse reaction (or miscarriage or spontaneous abortion), but the child/foetus does not experience any adverse reaction is created one case relatively to the parent.

The ICSR received from MAH, patients and healthcare professionals are saved in the database - SVIG. The database is also used to transmit case using XML to EudraVigilance and MAH that have electronic transmission system in place.

6.2.1 Adverse reaction reported from MAH

My first experience on the job was in the team responsible for the analyses and validation of adverse reaction received from MAH.

MAH mostly reports by electronic transmission (XML) as stated in the legislation. The cases should be completed following the ICH guideline E2B: Data Elements for transmission of individual case safety reports. However some MAH don't have electronic transmission and report using the CIOMS I format by letter, fax or email and the cases are introduced in the SVIG manually at DGRM.

MAH are responsible to collect every adverse reaction with the active substance under its responsibility, including the ICSR reported by healthcare professionals, patients and those in the medical/scientific literature. MAH only reports to DGRM the ICSR considered serious and the non-serious cases that have the expediting report condition. The cases should be reported to DGRM within 15 days. Each case has its own identification number (WWID) which identifies the case even after the case has received follow-up information.

Once the case is reported, it should be accepted in the database by a technician, who is responsible for verify the minimum criteria and send the acknowledgment (ACK) to MAH. The ACK should be sent in two days:

- ACK 01- valid message
- ACK 02- non-valid message
- ACK 03 - the message itself is not correctly formatted

After the reception of the case it is performed the duplicate search to verify any duplicate cases (same ISCR sent by different reporters) in the SVIG. Then is verified the priority of the case. High-priority cases includes the cases that results in dead, hospitalization or is life-threatening. High-priority cases requires for a pharmaceutical and causality assessment more urgent.

The pharmaceutical assessment includes the quality assessment and consists in verifying the different section in SVIG. Usually the MAH doesn't have all the information to fill the entire sections of an ICSR of the database, however some information are important to permit the

scientific assessment and should be verified. The Table 1 indicates in each section of the SVIG which are the critical information to be verified.

Table 1: Critical information to evaluate in each section

Sections	Important information
Administrative section	Origin of the case (Portugal) Seriousness criteria and immediate reporting Medically confirmed
Sender	Company's ID
Reporter	Qualification
Patient	Initials/gender/age/age group/
Medicine	Active substance or commercial name as suspected or interaction
Adverse reaction	Adverse reaction in MedDRA Lowest Level Term (LLT) Outcome of the reactions

For biologics medicines or vaccine it's important to verify if the batch number and if the commercial name is reported for better identify the safety signals and associate the ADR to the drug. If the seriousness criterion is death, at least one of the AR should have the outcome death and the case should contain the autopsy report, if available. If it's known by the reporter should be identified the concomitant drugs, in the medicines' section. The concomitant drugs are identified by active substance or commercial names. It is also important contain the date of administration and the posology used. The menu correspondent to the adverse reaction should contain the date and duration of the adverse reaction, and if the reaction is described in SmPC to permit the causality assessment.

If the MAH has the information available and if it is important to the scientific assessment of the case, the information about the clinical and pharmacological history is filled in the respective sections.

The annexes sections of the SVIG contain information about duplicate cases and related cases. Related cases are cases that can be evaluated as one or cases that influence the assessment of the

others; this includes for example cases of mother and child where both had reactions. The cases are identified by the WWID.

Each case should contain a narrative, where the case is described with more details. The information contained in the narrative should match the structured information of SVIG. The narrative can be written following the template of CIOMS V. It's important to read the narrative to comprehend the case and assess if it's necessary to request for additional information.

In case of any important information is missing it's possible to request follow-up information to the MAH. The serious cases should be transmitted electronically to EudraVigilance in 15 days. After the pharmaceutical assessment the cases are submitted to clinical assessment by the physician of DGRM, the physicians are responsible to make the causality assessment for each adverse reaction.

6.2.2 Adverse reaction reported from healthcare professionals and patients

The team is responsible for the assessment of adverse reactions reported from the healthcare professionals and patients received in the regional pharmacovigilance unit and for the processing of reports from Madeira and Azores.

The cases are reported using the notification form, email, letters or through the Portal RAM. The cases received from continental Portugal are inserted and processed in the Portal RAM by the pharmacovigilance regional unit concerned.

Once the case enters in the DGRM or in the regional units starts the clock to report the case to EMA via EudraVigilance. The serious cases are transmitted in 15 days and the non-serious cases in 90 days. The pharmacovigilance unit has 7 days to insert and process the case, and then send the case to SVIG. The pharmacovigilance unit is also responsible to determine the causality assessment. After the finalization of the case to SVIG, DGRM has 7 days to perform the pharmaceutical assessment, search for duplicates and transmit the case to MAH and the EudraVigilance if it is a serious ICSR. If it's a non-serious ICSR is only transmitted to the MAH in 90 days.

The cases are usually sent using XML, unless the MAH hasn't implemented the electronic transmission, and in this case, the ICSR is sent by email using the CIOMS I for serious ICSR and CIOMS II for the non-serious cases. When the cases are transmitted to EMA and to MAH the

confidentially agreement with the patient and the reporter is kept. The only information about the reporter transmitted is the qualification.

During the pharmaceutical assessment, is verified if the case need any additional information and it's requested additional information to the regional unit who is responsible to contact with the primary reporter to obtain the information. In case of major additional information it's altered the 'date of receipt of the most recent information for this report' and the case is transmitted again to MAH and EMA.

The ICSR reported from Azores or Madeira are processed by DGRM collaborators in the Portal RAM and then sent to SVIG when finalized. The analysis of the ICSR includes the search in the SmPC to verify if the adverse reaction is described (to determine the expectedness), determine the seriousness of the ICSR, elaborate the case narrative and contact the reported to confirm the information on the notification form and obtain additional information. Once the case is finalized to SVIG, it's then sent to the MAH and the EudraVigilance (if serious) in the established timelines.

The clinical assessment of these cases is performed by the clinical evaluator of DGRM. The physician uses the method of global introspection and the WHO scale (Table 2) to determine the causality and create the causality assessment report. The information about the causality term of each adverse reaction is inserted in the Portal RAM for each adverse reaction in the medicine's menu. The causality assessment consists in major additional information, therefore implies the insertion follow-up information in the case and alters the 'date of receipt of the most recent information for this report' and qualifies for reporting. The reporter is also informed about the causality assessment of the ICSR by email or letter.

Table 2: WHO Scale for causality assessment (62)

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)

	• Rechallenge satisfactory, if necessary
Probably/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

6.2.3 Adverse reaction associated to quality problems

DGRM may receive notifications in which the reporter suspects of a quality problem, in this case DGRM works in articulation with the Directorate for Inspection and Licensing (DIL).

If the notification does not contain an adverse reaction, it's forwarded to DIL which is the responsible Directorate to process the quality problem and perform the investigation.

In the other hand, if the case contains an adverse reaction and the reporter (or DGRM) suspects of a quality problem, the case is processed as an ICSR and the MedDRA term most closely to quality defect is included in the adverse reaction section. DGRM elaborates a report for investigation of suspected adverse reaction and send to DIL that will proceed with the investigation of the quality problem.

I participated in the entire tasks described, including the processing and transmit of non-serious cases and processing of serious cases. I was also involved in the processing of all the cases

received from the islands, including cases with a suspect of quality problem in which I elaborate the report for investigation.

6.3 Risk minimization

The risk minimisation team is responsible to evaluate and implement measures to minimize the risk associated to medicines. The activities include the direct health care communication, educational materials, evaluation of PSURs and RMP, safety variation and the response to NUI and RA. I will describe the activities performed in this group and the activities that I participated in.

6.3.1 Periodic Safety Update Report

Periodic safety update report (PSUR) is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance and the long-term effects of a medicinal product, during the post-authorization phase. The PSUR includes an evaluation of the safety, efficacy and effectiveness of the drug (63).

The MAH is responsible to re-evaluate the risk-benefit balance of its own medicines during the post-authorization phase and should submit the PSUR according with the following timelines previewed in the GVP VII (63):

- within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
- within 90 calendar days of the data lock point (day 0) for PSURs covering intervals in excess of 12 months;
- the timeline for the submission of ad hoc PSURs requested by competent authorities will normally be specified in the request, otherwise the ad hoc PSURs should be submitted within 90 calendar days of the data lock point.

To facilitate the submission and the evaluation of PSUR with the same active substance, was released the “EU reference dates (EURD) list” which contains the dates and frequency for submission of PSUR by active substance and combination. The EURD list contains the data lock point (DLP) and date of PSUR submission for each active substance (64). The DLP is the limit date of the data to be included in the PSUR.

The MAH prepares a single PSUR covering all medicinal products under his responsibility containing the same active substance. The PSUR covers information about all the use of the medicine, including, the off-label use, use during pregnancy, elderly and paediatric population and

gathers all the information available since the data lock point of the last PSUR and include studies or clinical trials in unauthorised indications or populations. The information contained in the PSUR includes the data from studies, medical use and spontaneous reports (63).

The PSUR should have the following structure, according to the Module VII of the GVP (63):

Part I: Title page, include the signature, name of the medicine and active substance, the reporting interval, MAH details, statement of confidentiality and date of report.

Part II: Executive Summary consists in a concise summary of the most important information contained in the PSUR.

Part III table of contents:

1. Introduction, where the MAH introduces the product, refers the international birth date (the date of the first MA for that substance) and describes the populations treated and studied.

2. World-wide market authorization status is a brief narrative overview including date of the first authorisation worldwide, indications(s), authorised dose(s), and where is authorised.

3. Actions taken in the reporting interval for safety reasons contain the significant actions related to safety that have been taken worldwide during the reporting interval, by the marketing authorisation holder, sponsors of clinical trials, data monitoring committees, ethics committees or competent authorities, which can influence the benefit-risk balance and impact the conduct of clinical trials.

4. Changes to reference safety information contain significant changes made to the reference safety information within the reporting interval, for example changes in contraindications, warnings, precautions, serious adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings.

5. Estimated exposure and use patterns refers to the information about the population exposed, including data about the volume of sales and prescription.

5.1 ***Cumulative subject exposure in clinical trials*** contains cumulative numbers of subjects from ongoing and completed clinical trials exposed to the medicine. It contains relevant information about the trials.

5.2 Cumulative and interval patient exposure from marketing experience should present the data in two categories: Post-authorisation (non-clinical trial) exposure, Post-authorisation use in special populations and other post-authorisation use.

6. Data in summary tabulations: contains safety data obtained from spontaneous reporting, from clinical trials and non-interventional studies.

6.1 Reference information specifies the version of the coding dictionary used for presentation of adverse events/reactions.

6.2 Cumulative summary tabulations of serious adverse events from clinical trials: provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the marketing authorisation holder's clinical trials, from the DIBD to the data lock point of the current PSUR.

6.3 Cumulative and interval summary tabulations from post-marketing data sources provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR. Includes AR obtained from spontaneous ICSRs and from solicited non-interventional ICSRs including those from non-interventional studies.

7. Summaries of significant findings from clinical trials during the reporting interval provide a summary of the finding obtained from clinical trials after the marketing authorization.

7.1 Completed clinical trials this section provides a summary of the data obtained from the completed trials during the reporting interval.

7.2 Ongoing clinical trials provide a summary of the data obtained from the ongoing trials during the reporting interval.

7.3 Long term follow-up includes data about the long-term follow-up of subjects from clinical trials of investigational drug.

7.4 New safety data related to fixed combination therapies includes information about the combination use of this medicine with other, if applicable.

8. Findings from non-interventional studies this section summarises information abtained in non-interventional studies that became available during the reporting interval.

9. Information from other clinical trials and sources

9.1 ***Other clinical trials*** contain information obtained from other clinical trial/study sources.

9.2 Medication errors contain data about medication errors, including information with no adverse event.

10. Non-clinical Data includes safety data obtained from non-clinical studies ongoing or completed during the reported interval.

11. Literature this section should include information about safety obtained from published or unpublished literature. Should include important information about ICSR of pregnancy, use in paediatric populations, lack of efficacy or important non-clinical safety results.

12. Other periodic reports apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSURs are prepared in agreement with the competent authority.

13. Lack of efficacy in controlled clinical trials includes data from clinical trials indicating lack of efficacy for products intended for life-threatening diseases.

14. Late-breaking information this section should contain important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PSUR

15. Overview of signals: new, ongoing or closed provide a high level overview of signals.

16. Signal and risk evaluation this section aims to provide summary of what is known about important identified and potential risks, the signals closed during the reporting interval, evaluation of new information about previous potential risks, summary of the effectiveness of risk minimisation activities.

16.1 Summary of safety concerns contains a summary of important safety concerns; it should include the following information important identified risks, important potential risks and missing information.

16.2 Signal evaluation contains the results of evaluations of all safety signals closed during the report interval.

16.3 Evaluation of risks and new information provide an evaluation of the new information about the previous risks and an update on important missing information.

16.4 Characterisation of risks contains the characterisation of the risks, including information about the frequency, numbers of cases, extent of use, estimate of relative risk, estimate of absolute risk and the public health impact.

16.5 Effectiveness of risk minimisation (if applicable). When a risk is identified can be implemented measures to minimize this risk, reducing the probability or the severity. This section should contain a summary of this information.

17. Benefit evaluation:

17.1 Important baseline efficacy and effectiveness information summarizes data about the efficacy and effectiveness.

17.2 Newly identified information on efficacy and effectiveness this section should contain new information about efficacy and effectiveness for authorized indication

17.3 Characterisation of benefits provide information to support the benefit-risk analysis, should provide a critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness.

18. Integrated benefit-risk analysis for authorised indications

18.1 Benefit-risk context - medical need and important alternatives contain brief description of the medical need for the medicinal product in the authorised indications and summarised alternatives.

18.2 Benefit-risk analysis evaluation contains the discussion of the benefit risk balance for each indication individually. This section also contains the methodology used to develop the benefit-risk evaluation.

19. Conclusions and actions include the implication of the new data, should include preliminary proposals to optimize further risk-benefit balance discussion, including proposals for additional risk minimisation activities.

20. Appendices to the PSUR contain the following appendices as appropriate**:**

- Reference information
- Cumulative summary tabulations of serious adverse events from clinical trials; and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.
- Tabular summary of safety signals.
- Listing of all the marketing authorisation holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.
- List of the sources of information used to prepare the PSUR.

I had the chance to read a number of PSURs and understand part of the process of evaluation. DGRM is responsible for the PSUR of the medicines authorized through national procedure, mutual recognition procedure, decentralized procedure and centralized procedure when Portugal is the Member-State responsible for the evaluation, in others cases the PSUR is archived. The PSUR are submitted to Infarmed using registered correspondence contained signed cover letter and one copy of the PSUR in electronic format (CD-ROM).

6.3.2 Risk Management Plan

During my period of internship at DGRM, I didn't have the chance to analyze an RMP, however I had to chance to read an RMP and understand the information that contains.

A Risk Management Plan (RMP) is one of the documents submitted for evaluation to obtain marketing authorization for the medicine and it's regularly updated with new information. It is a complete description of the Risk Management System of the medicine (65).

The risk management is a responsibility of the MAH and of the CA. Infarmed as a competent authority has the following functions (66):

- Monitor the benefit and the risks of medicinal products and take actions to minimize the risks and increase the benefits.
- Ensure the implementation of the risk minimization activities at national level.
- Inform the stakeholders about new safety data.
- Ensure than MAH of generics and similar biological medicines updates the risk minimization measures following the reference medicine.
- Provide information to other CA, including notification of any safety activity.

The aim of the risk management system is to ensure that the benefits of a medicine overweigh the risks, this risk-benefit balance can be changed, by reducing the risks or increasing the benefits, therefore the RMP contains information on how to manage the risks, but also specify the need for efficacy studies (66).

The RMP contains information about the characterization of the safety profile, plans for pharmacovigilance activities to characterize the known risks and identify new risks, plans to implement risk minimization activities and indication of how the effectiveness of those plans will be assessed (66).

The RMP should be submitted by the company at the time for marketing authorization application (MAA) and when requested by the NCA in case of a concern affecting the medicine benefit-risk balance (67).

The RMP template (Table 3) is set up in the GVP V. The RMP consists in seven parts, and the Part II is divided into 8 modules. The modules follow the titles in the Safety Specification of ICH-E2E. The risk management system is proportional to the identified risks and the potential risks of the product and the need for additional safety data.

Table 3: The RMP structure (66)

Part I Product(s) overview	Provide the administrative information and the overview of the product.
Part II Safety specification	• Module SI Epidemiology of the indication(s) and target population(s) • Module SII Non-clinical part of the safety specification • Module SIII Clinical trial exposure • Module SIV Populations not studied in clinical trials • Module SV Post-authorisation experience • Module SVI Additional EU requirements for the safety specification • Module SVII Identified and potential risks • Module SVIII Summary of the safety concerns
Part III Pharmacovigilance plan	Discuss the plans to identify and characterize the known safety concerns, the plan to investigate potential safety concern and plans to search for missing information.

	Routine pharmacovigilance activities Additional pharmacovigilance activities
Part IV Plans for post-authorisation efficacy studies	Provide a summary of existing efficacy data Plan for post-authorization efficacy studies (PAES)
Part V Risk minimisation measures	Routine risk minimization Additional risk minimisation activities Evaluation of the effectiveness of risk minimization measures
Part VI Summary of the risk management plan	Present a scientific summary of the RMP containing the information of the modules SI, SVIII and information of the part IV and V
Part VII Annexes	Interface between RMP and Eudravigilance/EPITT; Summary of product characteristics and package leaflet; worldwide marketing authorisation status by country; Synopsis of on-going and completed clinical trial programme; Synopsis of on-going and completed pharmacoepidemiological study programme; Protocols for proposed and on-going studies in categories 1-3 of the section "Summary table of additional pharmacovigilance activities" in RMP part III; Specific adverse event follow-up forms; Synopsis of newly available study reports for RMP parts III-IV; Details of proposed additional risk minimisation activities; Mock up examples in English; Other supporting data (including referenced material).

6.3.3 Direct Healthcare Professional Communications

A Direct Healthcare Professional Communications (DHPC) is a document used by the MAH or competent authority to transmit safety information to healthcare professionals. The DHPC contains information about measures and actions to consider relatively to the use of a medicinal product with the purpose of promote the safe and effective use (68).

The MAH and the CA works together to prepare the DHPC and they should agree about the content of information, the communication plan, the recipients and the timetable for disseminating of the DHPC (68).

The DHPC is disseminated in the situation of immediate action or change in the use of the medicinal product, for example suspension, withdrawal or revocation of the MA due to safety, restriction of an indication, new contraindication, change in the dosage, a new warning or

precaution, new data identifying a previously unknown risk, or new recommendation to prevent an adverse reaction (68).

The final DHPC can be published by the MAH as agreed with CA. The CA can also issue an additional safety announcement (68). The processing of the DHPC in Europe follows the indication of the GVP Module XV (Figure 9).

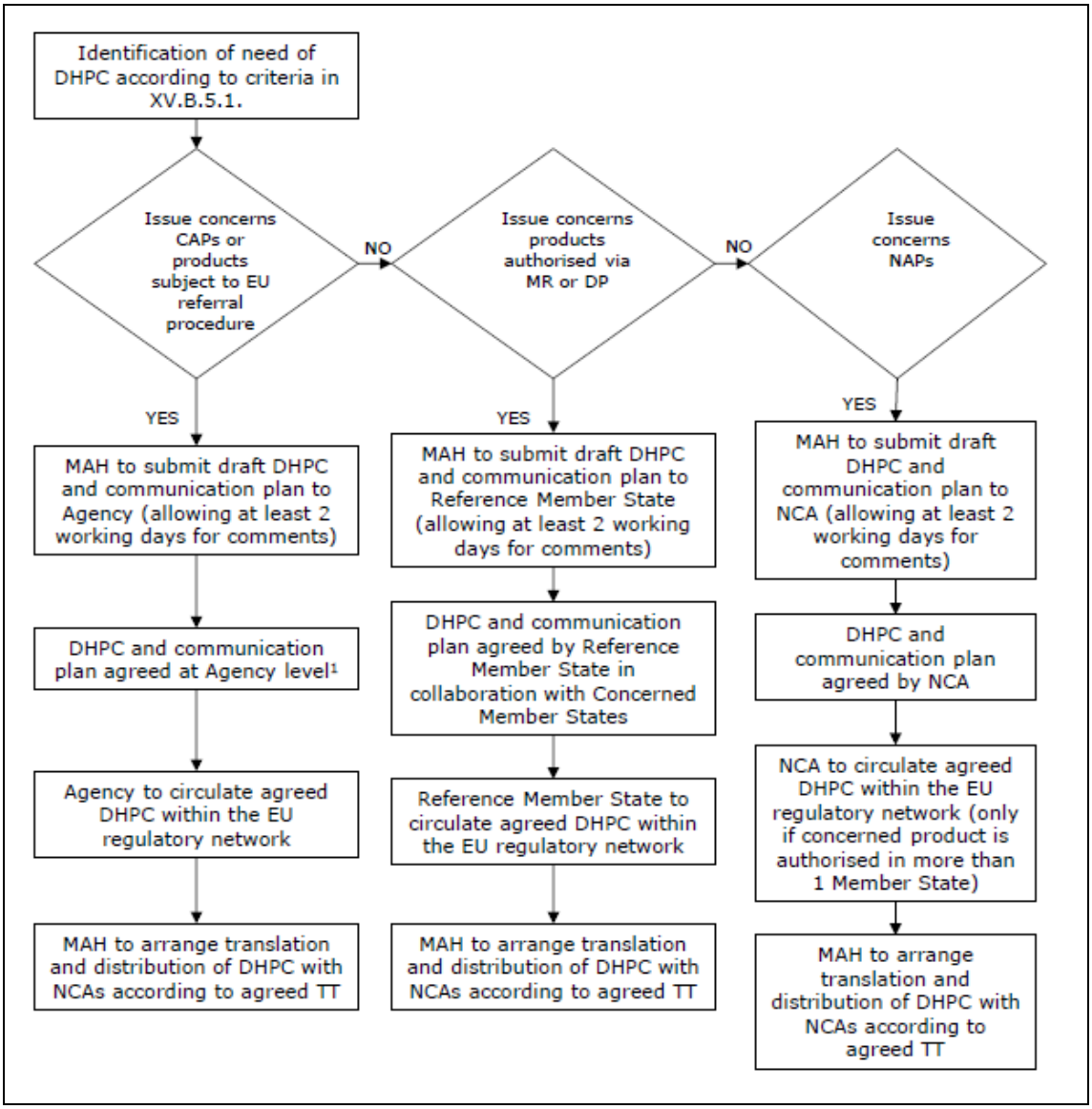

Figure 9: Flow chart for the processing DHPC in EU (68)

I had the chance to understand the process and validate DHPCs. When necessary the MAH submit a preliminary version of a DHPC to DGRM. The letter is validated considering the translation and the content taking into account the information in the SmPC and the applicable legislation. The

MAH and DGRM agree on the distribution universe and the distribution method. The letter in discussed with the head of the Directorate and then sent to the MAH. If the MAH agrees with DHPC the letter is then disseminated. Upon previous agreement with the MAH the letter is also published in the institutional website.

6.3.4 Educational Materials

Educational Material (EM) is an additional measure of risk minimization implemented when important or potential risks are identified for a medicine. EM aims to alert and inform healthcare professionals involved in the process of prescription or administration of medicines, and also inform the patients about the risks associated to a medicine. EM aims to increase the knowledge about specific risk, allow early detection and prevention of adverse reaction, increase knowledge about the measures to reduce the frequency and seriousness of ADR and inform healthcare professionals and patients (69).

The EM has a specific scope according to the risk to be addressed, the nature of the risk, and the specific steps taken by the professionals or patients to minimize the risks. The EM is based on the information contained in the risk minimization plan. The education material can give guidance about the prescription, can include information to patients and healthcare professionals about how to manage risk and how to notify adverse reaction of interest (70) .

During my internship I did not have the chance to participate on the evaluation procedure, however during the initial training I had the chance to comprehend the process of evaluation and implementation of EM.

6.3.5 Safety variations

A variation is defined as an alteration to the information contained in the SmPC and the PL. The variation classifications depend on the level of risk and impact on the quality, safety and efficacy of the product (71).

- Minor variation type IA – refers to a variation with minimal or no impact on the quality, safety or efficacy of the product (71).
- Major variation of type II – refers to a variation which is not an extension and has significant impact on the quality, safety or efficacy of the product (71).
- Minor variation type IB – refers to a variation which doesn't fulfil the criteria of minor variation of type IA or a major variation of type II or an extension (71).

DGRM is responsible for the management of safety variation in the terms of marketing authorizations classified into the category C.I.z) of the variations type IA_{IN}. These variations of type IA require immediate notification after implementation in order to ensure continuous supervision of the medicinal product. 30 days after the submission of the variation, it is given a tacit authorization. This variation includes the variations resulting from PRAC recommendation on signal analysis and should also be submitted as a variation classified into C.Iz) type IA_{IN} usually in 60 days after publication of the recommendation. The variations are submitted to Infarmed via electronic portal SMUH-ALTER (72).

During the internship I didn't have the chance to participate in any activity related to this procedure.

6.3.6 Informative circulars

After a PRAC or CHMP meeting is released an informative note to all Member State and each Member State is responsible to adapt the information to its reality and communicate with the general public. Infarmed publishes informative circulars to inform the healthcare professional, the MAH and the general public about recent information related to medicine, including safety information.

I had the opportunity to work with informative circulars during the internship. After the receiving the press release, DGRM is responsible to translate and adapt the information. During the preparation of the informative circular is important to consult the SmPC of the medicine and other sources if necessary. The preliminary informative circular is agreed with the head of Directorate and sent to Centre of Information about Medicines and Medical Products (CIMI) of INFARMED which review and verify the adequacy of the language. The final version is agreed with CIMI and the head of DGMR and is sent to the Directive Board for approval. After the approval of the Directive Board the informative circular is published in the institutional website. In the applicable situations, depending on the subject of the informative circular DRGM sends the informative circular to the appropriate receivers by email.

6.3.7 Rapid alert and Non-urgent information system

Rapid Alert (RA) aims to inform CA, EMA and EC about urgent and serious pharmacovigilance data related to medicinal product (73).

The RA is used by the Agency or MS when a safety concern which can potentially impact the benefit-risk balance or the public health arises. The RA arises when:

- Urgent safety restriction, suspension, revocation, or withdrawal of MA
- Recall of a medicine product from the market
- Actions for human blood and plasma derived medicinal products following occurrence of variant Creutzfeldt-Jakob disease in a blood donor.
- Important changes in the SmPC, including introduction of new contraindication, warnings, reduction of dose, restriction of an indication
- Inform immediately the healthcare professionals about a new risk

If a medicine authorized through national procedures, mutual recognition or decentralized procedure is target of suspension or revocation of the MA or important changes in the SmPC, the MS should inform the other MS using RA (73).

The Non-urgent Information (NUI) is used to exchange non serious information between MS and the Agency. A NUI can be used to:

- Inform on a potential new safety signal
- Inform on a status of implementation on regulatory action
- Inform other MS about important issues
- Request information
- Organisational matters;
- Facilitate data collection for interaction with external parties.

The answers to NUI are sent using the European Pharmacovigilance Issue Tracking Tool (EPITT) to all the MS and EMA. During my internship I had the opportunity to help preparing the answers to different NUI. The process to prepare an answer depends on the questions and include search in various sources, including the SmPC, list of AR, among others. The answer is approved by the head of the Directorate and then inserted in the EPITT.

6.4 Signal Management

Signal management refers to the activities performed to determine if a new risk associated to a medicine has aroused from the examination of ICSRs, data from active surveillance system, literature data or other sources. The signal management process includes initial signal detection, validation and confirmation, analysis and prioritization, signal assessment, and recommending action and exchange of information (74).

A signal is defined as information that arises and suggests a new potential causal association or a new aspect of a known association between an intervention and an event (74).

The sources of data to identify signals include AR reporting systems, active surveillance systems, non-interventional studies, clinical trials, scientific literature and others (74).

Signal detection: may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both (74).

Signal validation: is the evaluation of the data available to verify if there is sufficient information to support the causal association and further analyses. The process takes into account the clinical relevance and the previous awareness (74).

Signal analysis and prioritization: is the process of prioritizing signal that requires urgent attention and should be immediately managed due the significant public health impact. The prioritization process takes into account factors as the severity, reversibility, and potential for prevention of the clinical outcome, therapeutic alternatives, the strength of the evidence to support the signal, the clinical context, the public health impact, the increased frequency or severity of a known adverse reaction, novelty of the suspected adverse reaction, and if the medicine is under evaluation for marketing authorization (74).

Signal assessment: consists in evaluate the signal to identify the need for additional data collection or regulatory action. It is evaluated all the available data, including pharmacological, non-clinical and clinical data. The sources of information include the application dossier, literature, spontaneous ADR report, information of MAH and CA (74).

Recommendation for action: is a result from the assessment of the signal. The recommendation action include immediate measures, including the possibility of suspending the MA, need for additional information, periodic review of the signal, addiction investigation or risk minimization activities, update of the product information and PASS (74).

Exchange of information: the information on validated signals and the outcome of signal assessment should be exchanged between CA and MAH. The signals which are proved to be a new or changed risk and have impact on the benefit-risk balance should be communicated to the healthcare professionals and patients (74).

During my internship I wasn't involved in the activities on signal management. However I had the chance to intervene by filling ATC and DCI of the suspected medicines of the cases sent by the MAH.

The signal management, at DGRM process as described, the signal is detected using a multidisciplinary method. The signal evaluation process consists in the analyses of documentation to support the causal relationship, identification of additional information and implementation of actions.

6.5 Other tasks and activities

During the internship I had the chance to participate in the annual conference of Infarmed in which I could attend to important lectures to foster my knowledge in issues related to medicine and medical devices. I also had the chance to participate in training about Farmacoepidemiology, during this training I acquired knowledge about how to use epidemiology tools to comprehend the effect of medicine in the community and also comprehend the relationship between epidemiology and pharmacovigilance.

I had the chance to participate in the meetings of DGRM in which are discussed relevant topics, these meetings were very important to update about the activities developed at DGRM.

I was also able to participate in a project about the association of the Reye's syndrome and acetylsalicylic acid, this project was very challenging because it included an extensive research but it was also motivational and I found this important because I could participate in an activity with direct impact in the public health.

7 Discussion

During my internship I had the chance to comprehend and participate in the pharmacovigilance activities of a National Competent Authority. The pharmacovigilance activities can be divided in 3 interrelated parts: the monitoring though the analysis of ICSR, the detection of signals and the implementation of activities to minimize the risks identified. I had the chance to understand the 3 parts and participated in a various number of activities executed in each part.

The first team I was included in was responsible for the safety monitoring of medicines through collection, validation and scientific assessment of ICSR. My internship was more focused in the validation and processing of ICSR and I had the chance to participate in all the related activities and understand the relevance of ICSR in the pharmacovigilance. I was able to validate and process ICSR from the MAH, from the patients and healthcare professionals received through the regional units and from the islands.

The process of validating ICSR had some difficulties to me, mostly in the validation of ICSR from MAH because the cases sent are very incomplete, many sections in the SVIG are filled incorrectly and the case narrative is not organized. Sometimes I had difficulties to find what information I could ask the MAH for follow-up because some of the cases sent by the MAH are from literature and it was almost impossible to obtain follow-up information and I also had difficulty to find what information was important to the scientific validation.

The validation of ICSR from healthcare professionals and patients is easier because the pharmacovigilance units structure the information in the SVIG in the correct way and they always look to create an ICSR most complete as possible and if during the validation process I noticed that the case is missing an important information I could ask for the information to the pharmacovigilance unit and they contact with the primary source trying to obtain the information. I was involved in the complete processing of reports received from the island and that was one of the most challenge activities. The processing includes inserting the case in the Portal RAM and completing the entire sections of the case necessary to the scientific evaluation. I had to choose the MedDRA terms for the adverse reactions described by the reported and sometimes it's confusing to choose a term because MedDRA various terms that can be considered synonymous and I had to choose the term most representative of the adverse reaction reported to permit the signal managing. When I had doubt I would ask my colleagues including the physician of DGRM. Another challenge in processing the reports from the island was to verify if the adverse reaction is

expected or not because the SmPC sometimes doesn't contain the exact term described by reported but contains terms that may include the adverse reaction reported. The elaboration of the case narrative sometimes is also complicated because I had to introduce all the information important to the evaluation of the case and some information were not described in the notification form and I had to elaborate additional questions to the reporter.

Another important area of pharmacovigilance and one of the responsibilities of a national authority is to communicate with the healthcare professionals and protect the patients, informing them about the risks associated with medicines and implementing measures to reduce the risks. In terms of these activities I was able to participate in the validation of DHPC and elaboration of informative circulars. These activities were particular challenging because I had to understand the information that I should transmit and understand the background for that information, so I could validate the DHPC or process the informative circular.

The preparation of answers to NUI are also demanding and exhausting mostly because it is necessary an intensive research to obtain all the information necessary to answer the NUI and the answer is translated to English.

The minimization activities also involves the analysis of RMP and PSUR, in terms of these activities was I not very involved, I only had the chance to read some of those documents and see the structure. When reading the PSUR I verified that not all the MAH elaborates the PSUR following the structure set out in the GVP. Reading the PSUR and the RMP is very exciting because we can understand the whole process of the medicine development, the safety profile and the measures to protect the patients from harm.

During the internship I had to consult the GVP and the standard operational procedures (SOP) of DGRM which allow me to profound my knowledge and execute correctly the tasks assigned to me. I know understand better the GVP and the pharmacovigilance legislation, including their importance and practicality.

I found my academic base very important and most of the knowledge acquired was useful. The knowledge on the physiology and pathophysiology, the knowledge obtained about quality system and about the entire process of a drug development. The knowledge about pharmacovigilance activities, the NPS and the legislation and guidance applicable were particularly useful during the internship because they give me the background to understand the activities that I was participated in and were also useful during the preparation of this report. During my academic

journey I gain some important soft skills for example the autonomy and the critical sense which are skills important to develop the tasks that were assigned to me. For example the processing and validation of an ICSR requires critical sense to find what important information is missing and to verify the information with the reporter. The autonomy is very important and I think I became more autonomous during my internship, when I had a doubt I first read the procedures and the GVP to try to understand and then ask the opinion of my colleagues.

In terms of learning outcomes, I can say that I achieve almost all of my established outcomes. However I know this is just the beginning and I have to continue to work to fully understand the pharmacovigilance activities and legislation. I consider myself autonomous in terms of ICSR processing and validation, I comprehend the role of Infarmed in terms of risk management and how it interacts with the other pharmacovigilance partners and I understand the legislation better. However, one of my objectives, was to comprehend and be able to validate risk minimization measures and I consider that I did not completely achieve this outcome, because I didn't had the opportunity to validate educational materials and my work with validation of DHPC was limited.

My communication skills were improved due the constant communication I had with my colleagues at DGRM and due the communication with the pharmacovigilance units when requesting for additional information or clarifying doubts.

I learned how to do time management more perfectly throughout the internship due the variety of tasks assigned to me and their different demand degrees. Therefore I learned the importance of prioritizing tasks according with their demanding degrees and timelines. For example, there were times when I had non-serious cases to validate and at the same time I had to process an informative circular and I had to prioritize the informative circular because the deadline is stricter and demands more work.

I understand the importance of teamwork and how to be an active member of a team. DGRM works in teams and I was part of the team therefore I learned to work with my colleagues in different tasks for example when responding to a NUI or when processing ICSR. Team work revealed to be an efficient way to work and deliver results.

8 Conclusion

This report summarizes all the activities and the learning outcomes of 9 months curricular training at DGRM to obtain master degree in Pharmaceutical Medicine. I chose this curricular training because I wanted to understand the role of a national competent authority in pharmacovigilance and because I have always been interested in pharmacovigilance and drug safety.

This internship allowed me to improve my skills and my knowledge acquired during the academic journey. I consider this internship very relevant to conclude the academic training because it complements the theoretical knowledge acquired in the classes and gives an insight of the professional world. The internship allowed me to consolidate my knowledge and to learn new things about pharmacovigilance.

I had some difficulties during the internship but I overcome them by reading and asking for my colleagues help, therefore I think I evolve in the professional level. During the internship I had the chance to verify my weak points and to correct them but also I had the chance to strengthen my positive skills.

I appreciate the opportunity given to realize the internship and learn more about pharmacovigilance. Now I truly understand the importance of pharmacovigilance and I hope I can start my professional carrier in pharmacovigilance and do the best I can to promote public health.

9 References

1. European Commission. The EU pharmacovigilance system. [29 April 2014]; Available from: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm#geninf.
2. Herdeiro MT, Ferreira M, Ribeiro-Vaz I, Polónia JJ, Pereira AC. O Sistema Português de Farmacovigilância. Acta Médica Portuguesa. 2012;25(4):241-9.
3. WHO. Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre2000. Available from: http://apps.who.int/medicinedocs/en/d/Jh2934e/3.html.
4. Teixeira F. Aspectos Históricos da Farmacovigilância. Farmacovigilância em Portugal. 2003:20-38.
5. Mann RD, Andrews EB. PHARMACOVIGILANCE. John Wiley & Sons Ltd, editor2007.
6. Ray A, Gulati K. Current Trends in Pharmacology: International Union of Pharmacology; 2007.
7. Routledge P. 150 years of pharmacovigilance. Lancet. 1998;351(9110):1200-1. Epub 1998/06/27.
8. FDA. Federal Food and Drugs Act of 1906 (THE "WILEY ACT"). [01 August 2014]; Available from: http://www.fda.gov/regulatoryinformation/legislation/ucm148690.htm.
9. FDA. Sulfanilamide Disaster. [01 August 2014]; Available from: http://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm.
10. Lachmann PJ. The penumbra of thalidomide, the litigation culture and the licensing of pharmaceuticals. QJM : monthly journal of the Association of Physicians. 2012;105(12):1179-89. Epub 2012/08/22.
11. FDA. Kefauver-Harris Amendments Revolutionized Drug Development. [01 August 2014]; Available from: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.htm.
12. Avorn J. Learning about the safety of drugs--a half-century of evolution. The New England journal of medicine. 2011;365(23):2151-3. Epub 2011/12/14.
13. Emanuel M, Rawlins M, Duff G, Breckenridge A. Thalidomide and its sequelae. Lancet. 2012;380(9844):781-3. Epub 2012/09/04.
14. Widukind L. Deformities in children after prescribed drug use during pregnancy? 961;86: 2555.
15. McBride WG. Thalidomide and congenital abnormalities. The Lancet. 1961;278:1358.
16. Silva JCd, Soares MA, Martins SdO. Reações Adversas a Medicamentos Análise da base de dados do Sistema Nacional de Farmacovigilância (SVIG). Faculdade de Farmácia da Universidade de Lisboa. 2012.
17. WHO. The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products. 2002 [01 August 2014]; Available from: http://apps.who.int/medicinedocs/en/d/Js4893e/3.html.
18. Sultana J, Cutroneo P, Trifiro G. Clinical and economic burden of adverse drug reactions. Journal of pharmacology & pharmacotherapeutics. 2013;4(Suppl 1):S73-7. Epub 2013/12/19.
19. Pillans PI. Clinical Perspectives in Drug Safety and Adverse Drug Reactions. Expert Review of Clinical Pharmacology. 2008;1(5):695-705.
20. Strengthening pharmacovigilance to reduce adverse effects of medicines. 2008; Available from: http://europa.eu/rapid/press-release_MEMO-08-782_en.htm.
21. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15-9. Epub 2004/07/03.

22. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which drugs cause preventable admissions to hospital? A systematic review. British journal of clinical pharmacology. 2007;63(2):136-47. Epub 2006/06/29.
23. INFARMED. Notificações de RAM recebidas no SNF [05 August 2014]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/EVOLUCAO_1992_2011/Notificacoes_de_RAM_recebidas_SNF.pdf.
24. INFARMED. Notificações de RAM recebidas no SNF, por origem: médicos, farmacêuticos, enfermeiros, utentes e indústria. [05 August 2014]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/EVOLUCAO_1992_2011/Notificacoes_de_RAM_por_origem.pdf.
25. Guerra LN, Clérigo MI. Relatório anual 2013 Notificações e Casos de RAM recebidos no SNF. INFARMED; 2014 [5 August 2014]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/RELATORIOS_ANALISE_PERIODICA_DADOS/Relatorio%20anual.pdf.
26. INFARMED. Sistema Nacional de Farmacovigilância (SNF): Notificações e Casos de RAM - 1ºT/2014 2014; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM/RELATORIOS_ANALISE_PERIODICA_DADOS/Relatorio_1_T_2014_publicacao_casuistica_final.pdf.
27. Fors S-L. Nine million. Uppsala Reports 66 – July 2014. 2014.
28. EMA. Guidelines on good pharmacovigilance practices (GVP) 2014; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/04/WC500165571.pdf.
29. EMA. Implementation of the pharmacovigilance legislation. [1 August 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000520.jsp&mid=WC0b01ac05804fa031.
30. European Commission. DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010. 2010.
31. EMA. Medicines under additional monitoring. [cited 1 August 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp&mid=WC0b01ac058067bfff.
32. EMA. Questions and Answers to support the implementation of the Pharmacovigilance legislation - UPDATE. 2012.
33. EMA. European Medicines Agency publishes first summary of a risk-management plan for a medicine. 2014 [11 October 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/03/news_detail_002041.jsp&mid=WC0b01ac058004d5c1.
34. Nova legislação europeia de farmacovigilância. [13 August 2014]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOVA_LEGISLACAO_FARMACOVIGILANCIA.
35. DIRECTIVE 2011/62/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 8 June 2011.
36. INFARMED. Apresentação. [24 April 2014]; Available from: http://www.infarmed.pt/portal/page/portal/SOBRE_O_INFARMED/APRESENTACAO.
37. INFARMED. Medicines and health products regulatory authority. 2014; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/ABOUT_INFARMED.

38. Pêgo A. Infarmed: Um olhar sobre o presente, uma visão para o futuro. INFARMED, editor2013.
39. Portaria n.º 267/2012 de 31 de agosto, Diário da República - 1ª série - nº 169 (2012).
40. INFARMED. Direcção de Gestão do Risco de Medicamentos (DGRM). 2014 [1 May 2014]; Available from: http://www.infarmed.pt/portal/page/portal/SOBRE_O_INFARMED/ESTRUTURA_E_ORGANIZACAO/DGRM.
41. INFARMED. Infarmed – Autoridade Nacional do Medicamento e Produtos de Saúde I.P. - Manual da Qualidade MQ-02.
42. Decreto Lei nº 20/2013 de 14 de fevereiro, Diário da República - 1ª série - nº 32, (2013).
43. EMA. About us. [24 April 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000235.jsp&mid=.
44. EMA. What we do. [24 April 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&mid=WC0b01ac0580028a42.
45. EMA. Mission statement. [24 April 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000106.jsp&mid=WC0b01ac0580028a44.
46. EMA. Pharmacovigilance Risk Assessment Committee (PRAC). [24 April 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp&mid=WC0b01ac058058cb18.
47. EMA. PRAC: Overview. [24 April 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000538.jsp&mid=WC0b01ac058058cb19.
48. EMA. Pharmacovigilance Risk Assessment Committee - Rules of Procedures. 2012.
49. EMA. EudraVigilance: Background information (FAQs). 2006 [11 May 2014]; Available from: http://eudravigilance.ema.europa.eu/human/EVBackground(FAQ).asp.
50. EMA. EudraVigilance. [24 April 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000239.jsp&mid=WC0b01ac05800250b5.
51. EMA. EudraVigilance access policy for medicines for human use 2011. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108538.pdf.
52. EMA. Committee for Medicinal Products for Human Use (CHMP). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp&mid=WC0b01ac0580028c79.
53. EMA. CHMP: Overview. [cited 24 April 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000095.jsp&mid=WC0b01ac0580028c7a.
54. ICH. What is the purpose of ICH? [27 April 2014]; Available from: http://www.ich.org/about/history.html.
55. ICH. About ICH. [27 April 2014]; Available from: http://www.ich.org/about/vision.html.
56. ICH. Work Products. [27 April 2014]; Available from: http://www.ich.org/products/guidelines.html.
57. CIOMS. About Us. 2013 [27 April 2014]; Available from: http://www.cioms.ch/index.php/about-us.
58. CIOMS. Drug Development and Use. 2013 [27 April 2014]; Available from: http://www.cioms.ch/index.php/2012-06-07-19-16-08/about-us/drug-development.

59. Introduction to the WHO Programme for International Drug Monitoring. [11 May 2014]; Available from: http://www.who-umc.org/DynPage.aspx?id=98080&mn1=7347&mn2=7252&mn3=7322&mn4=7324.
60. VigiBase. [11 May 2014]; Available from: http://www.who-umc.org/DynPage.aspx?id=98082&mn1=7347&mn2=7252&mn3=7322&mn4=7326.
61. EMA. Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products. 2012.
62. WHO. The use of the WHO-UMC system for standardised case causality assessment [1 March 2014]; Available from: http://who-umc.org/Graphics/24734.pdf.
63. EMA. Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1). 2013.
64. Introductory cover note to the List of European Union reference dates and frequency of submission of Periodic Safety Update Reports. 2014.
65. EMA. Questions and answers on the risk management plan (RMP) summary. 2014.
66. EMA. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 1) 2014.
67. EMA. Risk-management plans. [14 August 2014]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000360.jsp.
68. EMA. Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication. 2013.
69. INFARMED. Materiais educacionais. [3 May 2014]; Available from: http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/INFORMACAO_SEGURANCA/MATERIAIS_EDUCACIONAIS.
70. EMA. Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators. 2013.
71. COMMISSION REGULATION (EC) No 1234/2008 of 24 November 2008. 2008.
72. INFARMED. Circular Informativa N.º 231/CD/8.1.6 - Recomendações do PRAC decorrentes da avaliação de sinais de segurança. 2013.
73. VOLUME 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use. 2008.
74. EMA. Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management. 2012.