**Universidade de Aveiro**
**2013**

Secção Autónoma de Ciências da Saúde

**ANA CATARINA MARQUES CARVALHO GONÇALVES**

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

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

**o júri**

| | |
|---|---|
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| Vogal - Orientador | Licenciada Maria Alexandra Castro Lopo Morais Bessa Soares Pêgo, Diretora, Infarmed - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. |
| Vogal - Co-Orientador | Doutora Maria Teresa Ferreira Herdeiro, Professora Auxiliar Convidada, Universidade de Aveiro |

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**palavras-chave**

Farmacovigilância, reação adversa, gestão do risco, monitorização de medicamentos.

**resumo**

Este relatório é o culminar de 12 meses de constante aprendizagem na Direção de Gestão de Risco do Medicamentos.

Este estágio decorreu nas áreas da Minimização do Risco e da Monitorização de Segurança de Medicamentos de Uso Humano.

A minimização do risco centra-se em assegurar a segurança dos medicamentos através da monitorização e avaliação de segurança dos medicamentos a implementação de medidas de segurança adequadas aos riscos identificados, tais como a avaliação de materiais educacionais, implementação de alterações de segurança ao Resumo das Características dos Medicamentos e Folheto Informativo, acompanhamento e implementação de medidas urgentes de segurança e comunicação e divulgação de informação de segurança através da validação das *Direct Healthcare Professional Communications* DHPC, elaboração de Circulares Informativas e artigos para o Boletim de Farmacovigilância. Incluiu ainda as actividades de gestão dos Relatórios Periódicos de Segurança e de gestão do sistema de alertas europeu.

A área de monitorização de segurança centra-se em recolher e avaliar as notificações de casos de reações adversas recolhidas no âmbito do sistema nacional de farmacovigilância. Tem ainda a obrigação de enviar essa informação para os parceiros internos e externos e gerir todo processo de gestão de sinal.

O estágio em ambas as áreas mencionadas permitiu-me adquirir competências indispensáveis para o meu percurso profissional e permitiu-me compreender como funciona uma Autoridade Nacional do Medicamento e a sua interação com a indústria farmacêutica, com os profissionais de saúde e com os doentes.

**keywords**

Pharmacovigilance, adverse reaction, risk management, drug monitoring.

**abstract**

This report is the result of 12 months of constant learning at Directorate of Risk Management for Medicines.

This internship was held in the areas of Risk Management and Medicines Monitoring.

The risk management focuses on ensuring the safety monitoring of medicines through the monitoring and safety evaluation of medicines and implementation of safety measures appropriate to the identified risks, such as the evaluation of educational materials, implementation of safety variations to the Summary of Product Characteristics and Package Leaflet, monitoring and implementation of urgent safety measures and communications and dissemination of safety information through the validation of DHPC, press releases and articles for the Pharmacovigilance Bulletin. It also includes the activities of Periodic Safety Update Reports management and management of European Alerts.

The area of medicines monitoring aims to gather and evaluate the adverse reactions collected within the national pharmacovigilance system and disseminate safety information required for safe use of medicines. It has also the responsibility to send that information to internal and external partners and the manage signal detections and evaluation.

The internship in both areas allowed me to acquire skills necessary for my career and allowed to understand how a National Competent Authority functions e and how interacts with the pharmaceutical industry, healthcare professionals and patients.

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## Abbreviations

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

ADR – adverse drug reaction

GVP- Good Pharmacovigilance Practices

FDA – Food and Drug Administration

EMA – European Medicines Agency

WHO – World Health Organization

CHMP - Committee for Medicinal Products for Human Use

MAH – Marketing Authorization Holder

EU – European Union

MAA – Marketing Authorization Approval

DGRM – Direção de Gestão do Risco de Medicamentos

DIL - Direção de Inspecção e Licenciamento

ICSR – Individual Case Safety Report

CA - Competent Authority

SVIG – Base de Dados do Sistema de Vigilância

MedDRA – Medical Dictionary for Regulatory Affairs Activities

SUSAR – Suspected Unexpected Serious Adverse Reaction

EEA – European Economic Area

MS – Member State

RMP – Risk Management Plan

PRAC – Pharmacovigilance Risk Assessment Committee

SmPC - Summary of Product Characteristics

# 1. Introduction

This document is a description of the 12-month training at *Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.* (INFARMED, I.P.), in the Directorate of Risk Management for Medicines. This internship allowed me to develop some of the knowledge acquired in the degree and master through applying it in practical work.

The pharmacovigilance has an important role in the protection of the public health and in the continuous evaluation of the medicines' risks and benefits. This science went through several modifications in the last few years, with the creation of new legislation and recognition of its importance in the protection of public health. The importance of pharmacovigilance is due to the fact that when a medicine is in the phase of clinical research, it is evaluated in a controlled environment, where the volunteers are chosen according to certain requirements and narrow criteria (1). Once a medicine is on the market, it is available for the majority of the population and more precisely to certain special groups such as children, pregnant women, elderly and also in patients with concomitant diseases and medicinal products, therefore there will be new scientific data, including new and rare adverse effects that were not detected during clinical trials (1). Although the pharmacovigilance is present in the early stages of drug development, it assumes a major role during the post-approval phase, where the safety profile of the medicine will be in constant re-analysis. Therefore it is necessary that the new medicines may be monitored for their effectiveness and safety under real-life conditions post release. Thus the ultimate purpose of pharmacovigilance is to minimise, in practice, the potential for harm that is associated with all medicines (1).

To improve patient safety and public health, the pharmacovigilance legislation came into force in July 2012. It strengthens and rationalises the system for monitoring the safety of medicines on the European market. (2)

**The main objectives of pharmacovigilance are (3):**

- Increase safety and patient care in relation to the use of medicines, by creating systems that allow a better and faster detection of adverse reactions;
- Improve and foster the national systems in detecting problems related to the use of medicines and communicate those findings within the proposed calendars;
- Contribute to a better understanding of the adverse reactions mechanisms and thus develop strategies to prevent those from occurring;
- Prevention of harm and maximization of benefit;
- Stimulate the rational and correct use of medicines;
- Promote training in understanding and management of pharmacovigilance information.

## 1.1 Historic perspective – Pharmacovigilance

It is known since the antiquity that a drug has its risks, and therefore the benefits must overweight these adverse effects or at least they must be acceptable taking into account the severity of the disease. Safety and doing no harm are concepts that have been around since Hammurabi code (2200 a.C.) and then later in the Hippocrates oath (460-370 a. C.) (4). However took many years and some well-known disasters, which the most well-known is the thalidomide disaster, to officially create the pharmacovigilance.

With the socioeconomic and scientific "explosion" in the final part of the XIX century, the medicines and the food products were produced in an industrial and unsanitary manner, which collided with the publication of a several articles by Upton Beall Sinclair Jr. describing the poor and negligent production of meat in the Chicago butchers (4). This was probably one of the reasons for the creation and publication in the United States of America of the "Pure Food and Drug Act" legislation in 1906, that prohibited the fake advertisement and the obligation to reveal the content of the products, through labeling of contents and dosage of each one (4).

Later in the XX century, in 1938, the "Federal Food, Drug and Cosmetic Act" legislation was published and it stated that every manufacturer has to prove that its drugs are safe for human use before entering into the market, which resulted with the obligation to conduct pre-clinical toxicity studies. This law was approved due to a 105 dead from renal impairment as result of the use of elixir sulfanilamide (5). In the early 50s, the Durham-Humphrey Amendments were created in the United States and it determines that certain medicines should be sold only with a medical prescription (4).

Later in 1960s, the Kefauver-Harris Amendments were published, and it specified that before using a medicine in humans it has to undergo a series of pharmacological and toxicological studies to prove its safety and efficacy. This legislation was created due to the thalidomide disaster. This medicinal product became very popular as sedative for morning sickness in pregnant. However, in April 1961, obstetrician William McBride notice that the cases of a rare birth called phocomelia in babies whose mothers had used thalidomide in pregnancy. He required the interruption of the using of this drug at the Crown St. Women's Hospital, where he practiced and he also wrote of his concerns to Distillers, the company that sold the drug in Australia. He wrote another letter to a leading medical journal, The Lancet describing the relation between phocomelia and the consumption of thalidomide during pregnancy. The concern of McBride about this drug saved countless babies form being born with bird defects. (6)

Therefore, due to the thalidomide disaster in 1961 the first systematic international efforts were initiated to address drug safety issues (3). The non-existence of organized safety monitoring systems was the main cause of the 4 year interval between its entering into the market and the detection of the teratogenic effect of this drug, which result in hundreds of cases of phocomelia, which would have been avoided if an effective national and international monitoring system was implemented at the time of this disaster (7). Therefore the main lesson from thalidomide is that active systems for detecting hazards are needed and that the safety monitoring of a medicine should start long before it is on the market.

Later in 1963, the World Health Organization (WHO) organized a forum for discussion termed the Sixteenth World Health Assembly were the resolution (WHA 16.36) was adopted. This resolution reaffirmed the need for early action in regard to rapid dissemination of information on adverse drug reactions, and therefore it led, in 1968, to the development of an international project to construct a system for the detection of ADR of medicinal products, it was called: "International Program of Adverse Reaction Monitoring", which aimed to promote the fast dissemination of safety information, specially the information regarding adverse events (8) (3). This program was based on the previous experience of the 10 following countries: United Kingdom, United States of America, Federal Republic of Germany, Canada, Netherlands, Ireland, Sweden, New Zealand, Australia and Czechoslovakia (8). The World Health Organization centre was first established on 1968 in Alexandria in the USA, however it was then moved to Uppsala in Sweden in 1978, called "Uppsala Monitoring Centre – UMC" (4). The principal aim of this program is to manage the international database of ADR reports received from National Centres (3) (9). In this Centre the spontaneous reports of all member states are collected, processed and stored.

A WHO technical report on this program followed based on a consultation meeting held in 1971. (3) The principal achievement of the 1971 WHO consultation meeting was:

- to advocate establishment of national centres for drug monitoring,
- to provide guidelines, and
- to identify the contribution that national centres might make to the international system. (3)

In this meeting it was noted that involving the healthcare professionals, the systematic monitoring of populations, review of healthcare statistics and of drug utilization data and effective analysis of input data would be necessary for the achievement of pharmacovigilance objectives. (3)

Several systems were developed in WHO Member States in order to collect ADRs and evaluate them. The collection and analysis of these ADRs in a central database, would serve the important function of contributing to the work of national drug regulatory (3). The database controlled in UMC is called Vigibase and it is the WHO global individual case safety report (ICSR) database; it consists of reports of adverse reactions sent by each member of this program. National centres are requested to send to this database every ADR on a regular basis, at least quarterly; although the centres can report more frequently. (10)

In order to facilitate the communication between countries and to promote the rapid safety signal identification, the Uppsala Monitoring Centre established standardized reporting rules to all National Centres (3).

In the 1980s, the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with WHO, launched a program on drug development and use. CIOMS provided a platform for recommendation from stakeholders (policy makers, pharmaceutical manufacturers, government officials and academics) on the communication of safety information between regulators and the pharmaceutical industry. (3)

The number of National Centres participating in the WHO International Drug Monitoring Program has increased. The role of these centres has contributed to the awareness of adverse drug reactions as a public

health concern; as a result, pharmacovigilance has become more than a regulatory activity, having a major role to play in clinical practice and the development of public health policy (3). To this fact contributes the location of the national and regional centres, which in the case of Portugal, the regional centres are located in universities and hospitals, which allows a closer relationship between the reporters and the National Authority (INFARMED, I.P.). In fact by April 2013 over 8 million reports were contained in the WHO database, making it the largest and most comprehensive pharmacovigilance database in the world (10).
The growing number of Individual Case Safety Reports (ICSRs) sent to UMC since its creation till 2012 is presented figure 1 (11).

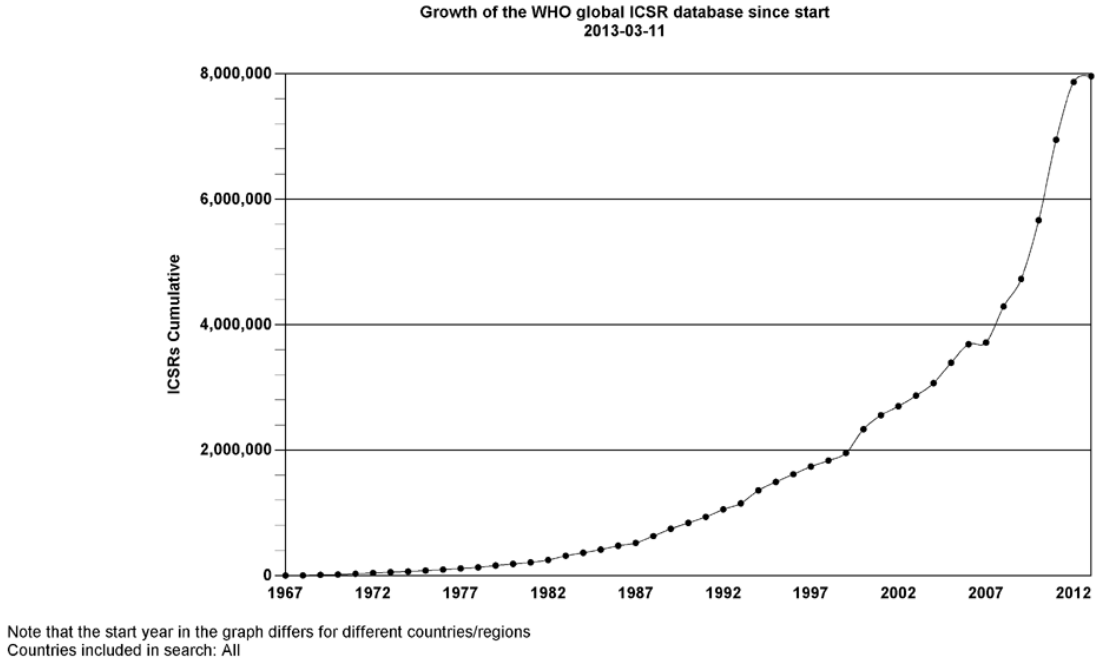



**Figure 1 –** Growth of the ICSR in WHO database since 1967 till 2012**.** (11)

According to WHO, the optimal Pharmacovigilance Centre (11):

- sends ICSRs frequently (monthly, or at least once a quarter)
- sends over 200 reports per million inhabitants per year
- sends reports from different areas - geographical and medical
- sends reports from vaccination and other public health programs
- sends reports containing traditional medicines (herbals)
- sends reports with as much information as possible
- has performed a causality assessment of the reports.

In order to regulate the activities related to medicinal product manufacturing, use and surveillance in Europe, the first European legislation regarding the use of medicines was the Directive 65/65/CEE of 26-01-

65. This Directive was a reaction to the Thalidomide disaster; it aimed to harmonize standards for the approval of medicines within the European Economic Community (12).

The Directive 75/318/EEC of 20-05-75, established the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (13). This directive wanted to bring the benefits of innovative pharmaceuticals to patients across Europe by introducing the mutual recognition procedure (13). The Directive states that Member States shall take all appropriate measures to ensure that the applications for marketing authorization are submitted by the applicants in accordance with the guidelines of the Directive(13). However it was the Directive 93/39/CEE of 14-06-93, amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products, that introduced major differences in terms of pharmacovigilance, which among other things, stated that each country should established its own pharmacovigilance system to capture the adverse reactions and to monitor all the medicines that are on the market, in addition, this directive also stated that the person responsible for placing the medicinal product on the market shall be required to record and to report all suspected serious adverse reactions which are brought to his attention by a healthcare professional to the competent authorities immediately, and in any case, at the latest within 15 days of their receipt. Also in the scope of pharmacovigilance, this Directive specified that Member States shall take all appropriate measures to encourage physicians and other healthcare professionals to report suspected adverse reactions to the competent authorities and impose specific requirements on medical practitioners, in respect of the reporting of suspected serious or unexpected adverse reactions, in particular where such reporting is a condition of the authorization. Therefore, when as a result of the evaluation of adverse reaction reports, a Member State considers that a marketing authorization should be varied, suspended or withdrawn, it shall forthwith inform the Agency and the person responsible for placing the medicinal product on the market. Thus, in case of urgency, the Directive indicated that the Member State concerned may suspend a medicinal product marketing, provided the Agency is informed at the latest on the following working day. (14) (4) (12) (13)

In Portugal, the first official rule was the Decree-Law nº 72/91 of 08-02-91- *Estatuto do Medicamento*. With the publication of this Decree-Law a new era in the national pharmaceutical sector begins, particularly in the field of marketing, quality control and manufacturing of medicines for human use. This document allowed to group every legislation on medicines of human use that were disperse, allowing the reorganization of this system in Portugal, with emphasis in quality assurance, safety and efficacy of medicines (15). In terms of pharmacovigilance, this document stated that the marketing authorization holders (MAH), physicians, pharmacies' technical directors and the other healthcare professionals, should communicate to *Direcção Geral de Assuntos Farmacêuticos* (DGAF) every adverse drug reactions that they become aware (15). DGAF was the regulatory body responsible for the study of the safety information and for the proposition of measures considered appropriate to protect the public health. The DGAF was responsible, since its creation in 1984, for the monitoring of the pharmaceutical practice, licensing of manufacturers, wholesalers and pharmacies, and for the marketing authorization approvals for human and

veterinary use. These were DGAF's responsibilities till 1993, when the Decree-Law N.º 10/93 of 15-01-93 determined the creation of INFARMED, I.P. (16) (17)

However, a year before, the National Centre of Pharmacovigilance was created as a result of the regulatory dispatch N.º 107/92 of 08-02-92. This dispatch also established the creation of the national pharmacovigilance system.

In the first years of the national pharmacovigilance system, healthcare professionals didn't collaborate with the system as much as in other countries of Europe. However, the numbers of ADR reports grew with the Ordinance 605/99 of 05-08-99, where the objectives, functions and organization of the National System were clearly defined, this ordinance also stated that the system is under the responsibility of the INFARMED and that pharmacovigilance regional units should be created, in order to decentralized the system and approach to the healthcare professionals and patients (4). According to this Ordinance, the objectives and functions of the National Pharmacovigilance System were (18):

- Collect, evaluate and disseminate information on the adverse drug reactions;
- Identify as early as possible reactions that may occur with the use of medicinal product;
- Examine and analyse, by processing the information and data collected, the possible existence of a causal relationship between certain medicinal product and an adverse reaction;
- Establish the most appropriate methods for obtaining data on adverse reactions;
- Systematically assess the safety profile of marketed medicinal products through the analysis of the relationship between risk and benefit of these medicinal products;
- Develop technical standards for the use of medicinal products and trigger action to reduce their risks;
- Collect data on consumption, as well as the misuse or abuse of drugs.

The growing numbers in ADR reports were due to the publication of the Pharmacovigilance bulletin and the healthcare professionals' education in pharmacovigilance. In fact the results several studies developed in the north region of Portugal, with the aim to analyse the effect of educational interventions in pharmacovigilance, showed that for both pharmacists (19) (20) (21) and physicians (22) (23) (24), face to face and regular education and qualification in pharmacovigilance is the key for higher rates for ADR reporting.

Although some authors defend that spontaneous reporting systems are not enough robust to promote safety detection, since many adverse reactions are missed due to lack of interest, willingness, availability, or awareness of stakeholders to report (25). This generates a lower number of reports collected, which does not represent the experience of patients compared to systematic collection (26). I

Therefore, information about ADR is limited and it does not represent the reality of adverse events resulting from drug use (19). The systematic collection of adverse drug reactions from patients may allow a better comprehension of the medicinal products safety profile, also providing a known dominator and a more comprehensive picture within a population. A program with the aim of actively sought for adverse

reactions was described in a paper by *Leone et al* (27). The program was implemented in pharmacies, where information was systematically elicited from patients who were engaged by their local pharmacists. (27) Although in the future, the programs of systemic collection of ADRs may be implemented to a larger scale in Portugal, the establishment of educational programs, even during university, may help improve the number of notifications. In fact this number has been growing in the last decade, and ultimately, it has already reached the number recommended by WHO of 200 reports/million inhabitants. The values reflected in figure 2, reveal that Portugal has become a very active country in the matter of pharmacovigilance. (28)

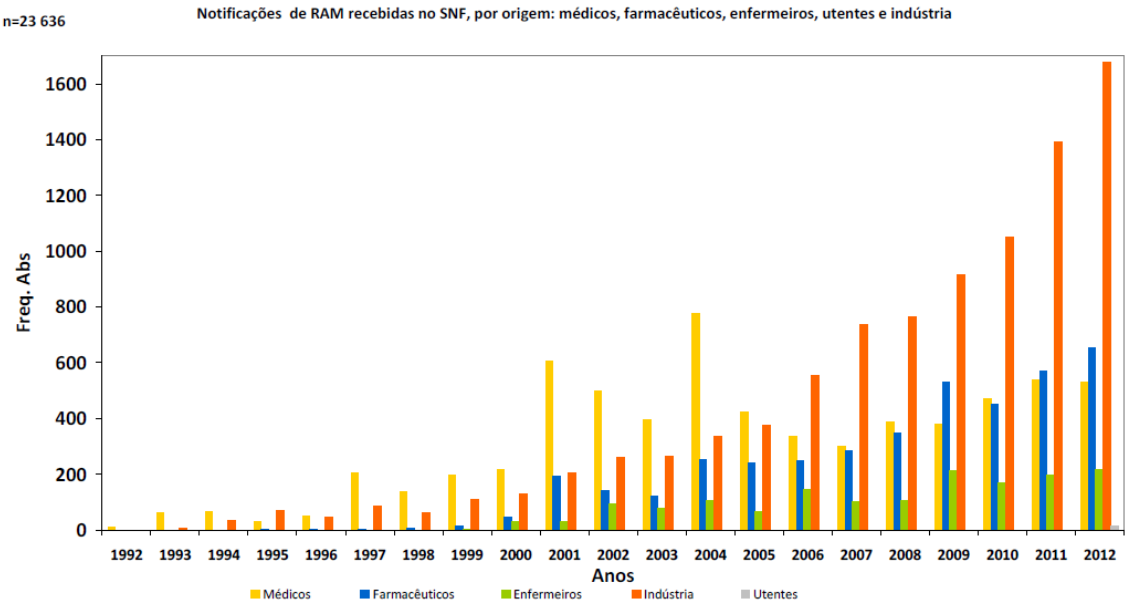



**Figure 2** - **Number of ADR reports received by source.** This graphic represents the evolution of the number of ADR reports since 1992 till 2012 in Portugal, sent by the pharmaceutical industry, consumers and healthcare professionals. (**Subtitles**: yellow marker: physicians; blue marker: pharmacists; green marker: nurses; orange marker: pharmaceutical industry; grey marker: consumers)

Over the years international legislation regarding pharmacovigilance changed in various ways. The Directive 2001/83/EC of the European Parliament and of the Council of 06-11-01 was created to describe the essential aim of any rules governing the production, distribution and use of medicinal products. This Directive concerns all medicinal products, although for pharmacovigilance it is most relevant to products authorised by the national, mutual recognition and decentralised procedures. The Member States are the licensing authorities in these procedures. In terms of pharmacovigilance, this Directive stated that the member states should maintain a national system for the collection of safety information of medicinal products, namely ADRs. This system should aim the evaluation of this information, in order to avoid or minimize the risks associated with medicinal products. The MAH should apply a system for risk management for each medicinal product; monitoring the results of risk minimization measures and maintaining the risk management system updated. This directive also foresees that a Marketing

authorization may be withdrawn, suspended, revoked due to the safety evaluation of pharmacovigilance data. It also describes the situations in which a member state initiates a process termed Urgent Union Procedure. These were only a few measures implemented with this Directive within the European Union. (29)

The Regulation N.º 726/2004 concerns centrally authorized products. The European Commission is the licensing authority for these products. In terms of pharmacovigilance, this Regulation increases the market safety surveillance by reinforcing monitoring procedures. It also stated that marketing authorization applications issued prior to 2 July 2012 were not obliged to implement a risk management system for each medicinal product. However, the Agency may nevertheless impose upon the holder of a marketing authorisation an obligation to implement such a system if it detects risks that might modify the risk-benefit balance of an authorised medicinal product. (30)

Over the past few years, both Directive Nº 2001/83/EC and Regulation Nº 726/2004 had several amending acts, in which the last ones were the new Directive Nº 2010/84/EC amending, as regards pharmacovigilance Directive 2001/83/EC on the Community code relating to medicinal products for human use and the Regulation Nº 1235/2010 amending, as regards pharmacovigilance of medicinal products for human use the Regulation (EC) No 726/2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and providing the legal basis for the European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. (31) (32)

In Portugal, the Decree-Law N.º 242/2002 of 05-11-02 was created to apply Directive 2001/83/EC of 06-11-01 to national law in terms of pharmacovigilance, it established the scope objective and organization of the national pharmacovigilance system. It also recognized the important roles of the healthcare professionals and the pharmaceutical industry in this system. (33)

Later in 2006, the Decree-Law N.º 176/2006 of 30-08-06 was approved, which unifies all applicable pharmaceutical legislation, including all pharmacovigilance aspects. (34) This regulatory paper, establishes the legal regime for marketing authorization and its amendments, the manufacture of medicinal products, import, marketing, labelling and information, advertising, pharmacovigilance, and use of medicinal products and their inspection. (34)

The Decree-Law N.º 20/2013 of 14-02-03 is the seventh amendment of the Decree-Law N.º 176/2006. The Decree-Law N.º 20/2013 aims to translate into national legislation the Directive 2010/84/EC, previously discussed. This Decree-Law introduced, in terms of pharmacovigilance, several changes that aim a to reformulate the National Pharmacovigilance System with the goal of a better detection, motorization and supervision of risks associated with the use of medicinal products (35).

Pharmacovigilance is now a dynamic clinical and scientific discipline, and it needs to develop further to meet public expectations and the demands of modern public health. (36)

Although Pharmacovigilance is a confidently established science, it faces some major challenges, such as the globalization, which allows populations to access to medicines at a larger scale. The wider access to the internet facilitates the dissemination of safety information that may not be accurate and it allows the selling

of medicinal products across national borders and even falsified medicinal products, which consists in one of the biggest risks for human health. The broader safety concerns are another major challenge of pharmacovigilance because there is a realization that adverse drug reaction may occur outside the terms of marketing authorization instead of within a specific dose range (the new definition of pharmacovigilance foresees the use within and outside the terms of marketing authorization). However these concerns and the acknowledgment of the harm caused by adverse reactions and the morbidity and mortality due these adverse reactions are finally being recognized as an important item on the European Community agenda. (36)

Pharmacovigilance has a crucial role in meeting the challenges posed by medicinal products. Therefore, it is essential that when adverse effects and toxicity do appear, especially when previously unknown, these are reported analysed and their importance and significance is effectively communicated to the consumers and healthcare professionals. The harm associated with a medicinal product can be minimized by ensuring that medicines of good quality, safety and efficacy are used rationally, and that the expectations and concerns of the patient are taken into account when therapeutic decisions are made. To accomplish this, there is a need to ensure that the risks are anticipated and managed, and this is achieved through the empowerment of consumers, making them a central piece in the system and to provide regulators with the necessary information to amend and improve the legislation and recommendations on the manufacture and use of medicinal products, improve communication between the health professionals and the public and educate health professionals to understand the effectiveness or risk of medicines that they prescribe. (36)

Therefore the description and analyses of the latest regulatory framework for pharmacovigilance is discussed ahead in this document.

## 1.2 State of the Art

Currently an ADR is one of the leading dead causes in many countries. It is estimated that 197,000 deaths per year in the EU are caused by ADRs and that the total cost to society of ADRs in the EU is €79 billion (37).
The Volume 9A was the main guideline for governing Medicinal Products in the EU (38); it contained the guidelines on pharmacovigilance for medicines for human use and it is divided in four parts. The first concerns the guidelines for marketing authorisation holders, the second, guidelines for competent authorities and the Agency, the third, guidelines for marketing holders, competent authorities and the Agency on electronic exchange of pharmacovigilance information in the EU, and the final part contains the guidelines for marketing authorisation holders and competent authorities on pharmacovigilance communication.
The new European Pharmacovigilance Legislation applies to all medicinal products authorised in the EU, independently the procedure used for their approval. The European Union legal framework for medicinal products for human use is given in Regulation (EC) No 726/2004 and Directive 2001/83/EC. However in terms of pharmacovigilance and as previously described, in December 2010, a new Pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) was adopted by the European Parliament and European Council, however they only came into force in July 2012.
The new legislation was created to make roles and responsibilities more clear, strength the EU network and ensure robust and rapid EU decision-making, to minimise duplication of effort, to increase the levels of transparency of procedures, to promote higher quality of safety data, and to make a proactive, science based and proportionate risk management. (39) It also promotes a greater involvement of consumers in the pharmacovigilance system, by engaging them in decision making and in the reporting of adverse reactions directly to INFARMED. (7) To achieve these objectives, several initiatives are being implemented with the new legislation, for instance, the network between EMA (European Medicines Agency), Member States, Pharmaceutical Industry, healthcare professionals and consumers is more clear and the involvement of each one of these stakeholders in the promotion of public health is reinforced. The role of the EMA in improving coordination between Member States is strengthened through the creation of new committee, the Pharmacovigilance Risk Assessment Committee (PRAC) (40). It was also clear that the responsibilities of MAHs for pharmacovigilance should be clarified. These responsibilities are described in the Directive 2010/84/EC, which states that MAHs should be responsible for continuously monitoring the safety of its medicinal products, for informing the authorities of any changes that might impact on the marketing authorization, ensuring that the product information is kept up to date, providing all available information, including the results of clinical trials or other studies, as well as reporting any use of the medicinal product which is outside the terms of the marketing authorization. (31) On the other hand Competent Authorities are empowered to enforce the collection of safety and efficacy information through post-authorization safety studies as a mandatory requirement to grant marketing authorization.

In order to minimize the duplication of effort, the coordination group should agree on a single position for pharmacovigilance assessments concerning medicinal products authorised in more than one Member State and in the case of products centrally authorized the European Commission is the regulatory body to decide and adopt harmonised measures. (31)

The new timelines for decision making for marketing authorized medicinal products, faster warnings, restrictions and improvements to product information, allow a stronger link between safety assessments and regulatory action.

To promote the high quality of safety data, the Commission in collaboration with the Agency, Competent Authorities and other stakeholders, should present an assessment report regarding the readability of the summaries of product characteristics and the package and propose, if necessary, changes and improvements in these texts. (31)

The definition of ADR was changed to become more comprehensive, it includes, besides the use within the marketing authorisation, the uses outside the marketing authorisation, since a considerable amount of adverse reactions occur when the medicinal product is used outside the terms of marketing authorization, the medication errors, overdose, abuse, misuse and occupational exposure (41).The new legislation determines that an ADR is a response to a medicinal product which is noxious and unintended (31). With the new legislation the MAH has to submit all ADR directly and only to EudraVigilance, however this will only be possible in 2015, when this database is fully ready to receive all notifications (41). These reports will be immediately forward to the Member State on the adverse reaction occurred. With this patients will also be able to notify without previous medical conformation. (41) These type of system where the consumers report directly to competent authorities all suspected adverse reactions were already operating in some EU Member States, notably the UK, Denmark and Netherlands, where their impact is positive (40).

There will be changes in the content and submission of periodic update safety reports and risk management plans to make them more rigorous, science-based approach that integrates the concepts of benefit-risk balance and risk-minimization measures, in order to make a proactive and proportionate risk management. To facilitate a single evaluation of PSURS with the same active substance or combination of active substances, the dates and frequency for submission of PSURs are harmonized, which avoids the duplication of effort and resources. (31)

With the submission of all ADRs directly to Eudravigilance, the scope of periodic update safety reports has changed to a benefit-risk analysis rather than just listing of individual cases. (31) The pharmacovigilance measures for risk management planned by each marketing authorization holder for each individual medicinal product, should be proportionate to the identified risks, the potential risks, and the need for additional information on the medicinal product. (31)

It is also one of the major goals of the new legislation to promote the transparency and openness, therefore each Member States will be obliged to set up and maintain national medicines web-portals with (40):

- Summaries of product characteristics

- Package leaflets
- Summaries of the risk management plans for authorized medicinal products
- The list of medicinal products that are subject to additional monitoring
- Information on the different ways of reporting suspected adverse reactions to the national competent authorities by healthcare professionals and patients

The national web-portals will be linked to a European medicines portal. This will include(40):

- information about the EMA Pharmacovigilance Risk Assessment Committee and its meetings;
- post-authorization study's conclusions;
- summaries of risk management plans;
- list of locations of the pharmacovigilance master files;
- information about Union reference dates and frequency of submission of periodic safety update reports;
- protocols and public abstracts of results of the post-authorization safety studies;
- information on the initiation of urgent union procedures (including the active substances or medicinal products concerned, the issue being addressed, any public hearings and information on how to submit information and participate in public hearings;
- the conclusions of assessments, recommendations, opinions, approvals and decisions taken by the PRAC and Committee for Medicinal Products for Human Use (CHMP) and by the Coordination Group, the national competent authorities and the Commission in the framework of assessment of periodic safety update reports.

Each medicinal product under additional monitoring will be identified by a black symbol and a standardized explanatory sentence in the summary of the product characteristics and in the package leaflet: " ▼ This medicinal product is subject to additional monitoring." These medicinal products are available in a European list of medicines under additional monitoring is available. A medicine remains under additional monitoring for five years or until the PRAC decides to remove it from the list. However a medicine can be included on this list when it is approved for the first time or at any time during its life cycle. (42) (31)

Some features of the new legislation will only be applicable over the coming years; therefore European Commission published the transitional arrangements concerning the entering into force of the new rules of pharmacovigilance.

## 2. Training Objectives

The objectives for my training are:

- To know how a regulatory authority for medicines works and how it articulates with the European Medicines Agency;
- To apply the multi-disciplinary background and the knowledge that was acquired during the biomedical sciences course and the master's degree course to the practice of a pharmacovigilance department at a regulatory authority;
- To acquire experience in medicines monitoring and risk management;
- To gain a deep knowledge about the pharmacovigilance legislation and procedures;
- To be actively involved in the directorate daily activities;
- To aim my personal and professional development;
- To contribute to the improvement of public health.

# 3. Vision about the host institution – INFARMED

INFARMED was created in 1993 with the promulgation of Decree-Law N.º 10/93 (16). It is the national authority responsible for the regulation of the sector of medicines, medical devices, cosmetic and body hygiene products, according to the high standards of public health protection. It assures the access to quality, effective and safe medicines, medical devices, cosmetic and body hygiene products by healthcare professionals and patients (43).

The main mission and duties of INFARMED are (44):

a) Contribute to the creation and development of the health policy, including the definition and implementation of policies for human medicines, medical devices, cosmetics and products for personal hygiene;
b) Ensure the regulation and supervision of research, production, distribution, marketing and use of human medicines, medical devices, cosmetics and products for personal hygiene, according to their jurisdictions;
c) Ensure compliance with the standards for authorization of clinical trials with human medicines, as well monitoring compliance with good clinical practice;
d) Ensure quality, safety, efficacy and cost-effectiveness of medicines for human use, medical devices and cosmetics and personal hygiene products;
e) Monitor the consumption and use of medicines and medical devices for human use;
f) Promote the access for healthcare professionals and consumers to information necessary for the rational use of medicines for human use, medical devices, cosmetics and products for personal hygiene;
g) Promote and support, in conjugation with universities and other research and development units, national or foreign, the study and investigation in the domains of science and pharmaceutical technology, biotechnology, pharmacology, pharmacoeconomy and pharmacoepidemiology;
h) Ensure proper integration and participation within the European Union system for the evaluation and supervision of medicinal products for human use, including coordination with the European Medicines Agency and the European Commission and other European Institutions;
i) Ensure the proper integration and participation within the network of national authorities responsible for medicines, medical devices and cosmetics and personal hygiene products of the European Union and within the network of official laboratories for medicines' validation of quality in Europe;
j) Ensure other international obligations of the State within its powers, particularly within the European Union, as well within the European Council and especially the European Pharmacopoeia

Commission and the United Nations in the area control of narcotic drugs and psychotropic substances;

k) Develop activities of national and international, bilateral or multilateral nature, within the scope of its responsibilities.

The activities performed by INFARMED, I.P. are presented in the next figure, it illustrates the life cycle of medicines and health products.


**Figure 3 –**Respresentation of the life cicle of a medicinal product, from its investigation till its use by the consumers. In this diagram the pharmacovigilance assumes a central role, since it is present in every phases of this cycle (45). (**Subtitles**: the first step of this life cycle is investigation and development followed by clinical trials; authorization, manufacturing, wholesale distribution, prescription, dispensation and utilization of a medicine. The fisrt grey marker is the technical and scientific evaluation and the second one is the reimbursement and economic evaluation).

## *3.1 Direção de Gestão do Risco de Medicamentos*

*Direção de Gestão do Risco de Medicamentos* (DGRM) is the directorate within INFARMED, responsible for the monitoring of the medicines with a marketing authorization in Portugal. It has the responsibility (46) of:

- Ensure the coordination and functioning of the National Pharmacovigilance System of Medicines for Human Use, particularly for the collection, evaluation and dissemination of information on suspected adverse drug reactions, for the analysis of causal relationship between medicinal products and adverse reactions and the early identification of safety problems with the use of medicines;
- Manage the European pharmacovigilance alerts system within the European Union and ensure the participation in the Program for International Drug Monitoring of WHO;
- Ensure the safety monitoring of medicines through the evaluation of risk management plans;
- Promote and conduct epidemiological studies, propose and implement safety measures and reports on benefit-risk;
- Coordinate the activities of pharmacovigilance units that integrate the National Pharmacovigilance System;
- Collaborate with other national and international entities in the promotion and performance of studies in the field of medicines epidemiology;
- Ensure the dissemination of safety information to health professionals and the general public;
- Ensure liaison with the Evaluation of Medicines Commission regarding pharmacovigilance, except in what regards Periodic Safety Update Reports;
- Collaborate in the activities of regulatory and scientific advice;
- Ensure coordination with national and European information systems within its competence;
- Ensure, within its mission, the representation of INFARMED, I. P., at a national and international level, including the EMA's Pharmacovigilance group and pharmacovigilance centers of other National Medicines Agencies.

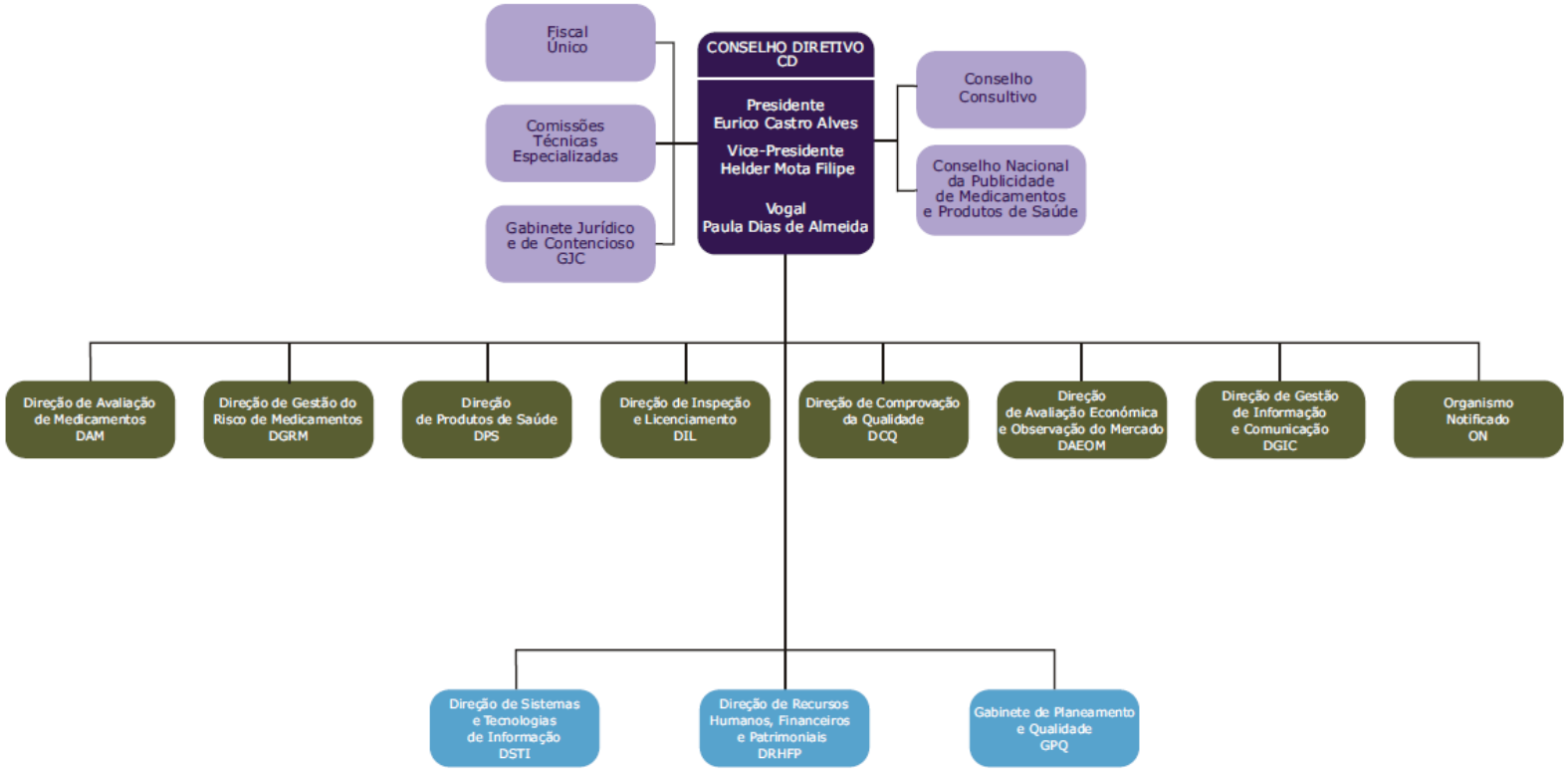



**Figure 4 -** INFARMED's organizational chart. (47)

## 3.2 INFARMED, I.P. Quality System

Quality is a responsibility share by all the Infarmed's Collaborators. To assure that procedures are implemented and executed in with the highest standards, a set of values were defined and implemented that are a guide in the process of decision making.

The Infarmed's Quality Policy is based on the following 4 principles (48):


**The processes are divided in 3 classes:**

**Planning and management processes**: processes related with the planning and monitoring of Infarmed's activity and system continuous improvement;

**Business processes**: processes related with the completion of a service;

**Support process**: processes that aid the business processes.

### DGRM Quality System

DGRM is one of the certified directorates in INFARMED. The certification is based on the NP EN ISO 9001:2008 – Requirements for Quality Systems. The quality system is based on the construction and

improvement of Standard Operating Procedures (SOPs), each one of these SOPs is developed by DGRM collaborators for each procedure.

The process designation for DGRM activities is Safety Monitoring and it described as the monitoring of safety of medicines for human use through the management and evaluation of the adverse reaction reporting, of the periodic safety update reports and other data with the purpose of detect and evaluate signals and communicate safety information.

# 4. Regulatory entities and groups that coordinate Pharmacovigilance

Besides the INFARMED, I.P. and more precisely DGRM, there are other important regulatory entities that act at an international level for coordination of Pharmacovigilance.

**European Medicines Agency**

The EMA is a decentralized agency of the European Union and it has the responsibility to protect and promote the public and animal health, through the evaluation and supervision of medicines for human and veterinary use (49). It is responsible for the pharmacovigilance of human and veterinary medicines, with strict collaboration with the European National Competent Authorities, such as INFARMED, in terms of evaluation of the quality, safety and efficacy of medicinal products that falls within the European legislation (49)

It provides the necessary input for efficient and transparent evaluation procedures to help bring new medicines to the market, through a centralized procedure for certain medicines. With this procedure the companies submit a single marketing authorization application to the Agency. (49)

The Agency also develops new strategies to promote the research and development of new medicines for public health needs and provides scientific advice and incentives to stimulate the development and promote the availability of new innovative medicines and ensure their benefits overweigh their risks. (49)

In terms of pharmacovigilance the Agency monitors the safety of medicines through a pharmacovigilance network, and it may take any appropriate action to protect public health, if any safety signal arises and it is suggested that the benefit-risk balance of a medicine has changed since it was authorized. (49) It also establishes guidelines and gives the most input for development of new legislation.

**EMA - EudraVigilance database**

EudraVigilance (EV) is a database that contains adverse reactions reports received from all the regulatory agencies within European Union and from pharmaceutical companies. It currently contains adverse reactions reports on authorized and licensed medicines from across Europe. This information is shared by national competent authorities (40) (50). It also allows the processing, management and evaluation of suspected adverse reactions. (51) (50)

It is one of the most important tools in pharmacovigilance, because it allows the evaluation of safety signals at a bigger scale, since it collects all the ADR from EU.

It is stated in the new legislation that since July 2012, the role of Eudravigilance is expanded: It has become the single point of receipt for all pharmacovigilance information for medicines for human use authorized in the EU. Companies and Member States will report reactions directly to

Eudravigilance, which will immediately notify all Member States electronically. However this database is not ready to receive all adverse reaction from the UE, therefore the direct sending of ADRs from MAH to EV will be fully implemented in 2015. (40)

EudraVigilance supports the (50):

- Electronic exchange of suspected adverse reaction reports (referred to as Individual Case Safety Reports) between the EMA, National Competent Authorities, MAH, and sponsors of clinical trials in the EEA;
- Early detection of possible safety signals associated with medicinal products for Human Use;
- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions;
- Decision making process, based on a broader knowledge of the adverse reaction profile of medicinal products especially in the frame of Risk Management.

**Committee for Human Medicinal Products**

The CHMP is responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use. It can also provide and request opinions to other committees and working parties. (52)
In matters of pharmacovigilance, the committee responsible for the evaluation of the safety information is the PRAC. However it shall transmit any recommendation to CHMP for adoption. Till July 2012, the Pharmacovigilance Working Party (PhVWP) was the entity responsible for the evaluation of safety information, however since this date it was replaced by PRAC. (52)

**Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human**

The CMD(h) (Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human) is a group established in 2004, to provide and examine any question related to marketing authorizations through mutual recognition or decentralized procedures (53). Its role is to consider cases of disagreement between Member States involved in a mutual recognition or decentralized procedure on the assessment report, the summary of product characteristics, the labeling or the package leaflet on the grounds of "potential serious risk to public health". (40)

This group has as its priority to collaborate with PRAC to make recommendations and propose actions in relation to risk management strategies for products approved through mutual recognition and decentralized procedures (53).

**Pharmacovigilance Risk Assessment Committee**

The PRAC is the committee responsible for the evaluation of the safety information, and therefore it carries out most of the Agency's work on pharmacovigilance (54). Several experts from each of the national authorities in Europe are part of it, as well specialists of each scientific area that give inputs and opinions in several issues (54).The PRAC will advise the Coordination Group and the CHMP on all aspects of the assessment of pharmacovigilance data after the authorization of a medicine (40).

It assesses all aspects of risk management of medicines for human use, which includes detection, assessment and evaluation of all adverse reactions to medicinal products and subsequent risk communication. It is also responsible for the design and evaluation of pharmacovigilance audit and post-authorization safety studies. (40)

**World Health Organization**

WHO has a major role in the pharmacovigilance at an international level. This organization is responsible for coordinating and directing the health system within its country members. It is also responsible for providing leadership for health questions and issues at a global level, and determining the world health agenda, setting norms and standards, providing technical support to countries and monitor and assess health trends. (55)

WHO developed the Program for International Drug Monitoring, that aims is monitor the safety profile of a medicine at an international level. The operating centre of this initiative is at Uppsala Monitoring Centre (UMC). The main goal of this Centre is to protect public health and to improve patient safety and welfare by reducing the risk of medicines (8). Several centers work with UMC, by collecting all suspects of adverse reactions, and then sending them to UMC for entry into the WHO database. (10) The WHO's database is the VigiBase and it is the global ICSR database; it consists of reports of adverse reactions received from the countries that are registered in this program. (10)

**International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use**

The ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) is a joint initiative between Industry and Authorities as partners in discussion, to ensure safety, quality and efficacy of drugs. ICH's mission, as stated in its site, is "*to make*

*recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines. "*
The ICH was created after the demonstration, in 1980 by the European Commission, that harmonization in regulatory and scientific development of a new medicine, was possible and needed. Therefore plans for creating ICH were made at the WHO Conference of Drug Regulatory Authorities, in 1989. The official creation of this Conference took place at a meeting in Brussels in 1990. Attending to the meeting were representatives of regulatory authorities and industry associations of Europe, Japan and USA. (56)
So far many guidelines have been created to ensure safety, effective and high quality medicines. These technical documents have been developed to prevent the duplication of work and efforts, promote public health, prevent unnecessary duplication of clinical trials in humans, and minimize the animal testing. (56)

**Council for International Organizations of Medical Sciences**

CIOMS (Council for International Organizations of Medical Sciences) is an international non-governmental organization established by the World Health Organization and by the United Nations Educational, Scientific and Cultural Organization (UNESCO). It represents de biomedical scientific community (57)
The objectives of this organization are (57):

- Facilitate and promote international activities in the field of the biomedical sciences.
- Collaboration with the United Nations and its agencies
- Serve the international interest of international biomedical community.

It has several work groups, which are responsible for the analysis of several topics in pharmacovigilance. The more important working groups are CIOMS I (reporting adverse drug reactions); CIOMS II (Preparation of periodic safety update reports); CIOMS III (Rules for Company Core Safety Information); CIOMS IV (benefit-risk assessments); CIOMS V (practical issues in pharmacovigilance); CIOMS VI (clinical trial safety data); CIOMS VII (development safety update reports); CIOMS VIII (Practical Aspects of Signal Detection in Pharmacovigilance); CIOMS IX (Practical Considerations for Development and Application of a Toolkit for Medicinal Product Risk Management); CIOMS X (Considerations for applying good meta-analysis practices to clinical data within the biopharmaceutical regulatory process). (57)

# 5. National Pharmacovigilance System

As already described, the national system of pharmacovigilance was created in 1992 (4). It was established by the Decree-law N.º 72/91, which states that the MAH, physicians, pharmacies technical directors and other healthcare professionals should communicate to INFARMED, all ADR that occurred due to the intake of a medicinal product. In the years following the publication of this Decree-Law, an effort to improve the system was made, by introducing more human and material resources and through the dissemination of the system and notification forms to healthcare professionals and through the participation in international pharmacovigilance groups, such as PhVWP. (4)

Later, the system was decentralized, to combat the under-notification of ADR; four regional units were created. Also with the aim to expand and develop the system, Portugal was involved in the development of adverse drug reactions database, being the first Member State to use the then new electronic transmission system of pharmacovigilance data (Eudravigilance). (4) (18)

The main source of information in the national pharmacovigilance system is based on the spontaneous reporting of cases of adverse reactions by the healthcare professionals, MAH and consumers. (7)However the sources of the pharmacovigilance information are diverse, therefore it also includes clinical and epidemiological studies, literature, data bases, additional monitoring of medicines, surveillance programs, etc (4). Both serious and non-serious reactions should be reported, since is this type of information that may change the benefit risk balance of a medicine and it also contributes for a deeper knowledge of a medicines safety profile. These notifications may be sent to the Regional Units or directly to DGRM, they can also be sent to marketing authorization holders, which in this case these notification should be sent to INFARMED for safety analysis (4). After the reception and treatment of each notification, a causality assessment is performed.

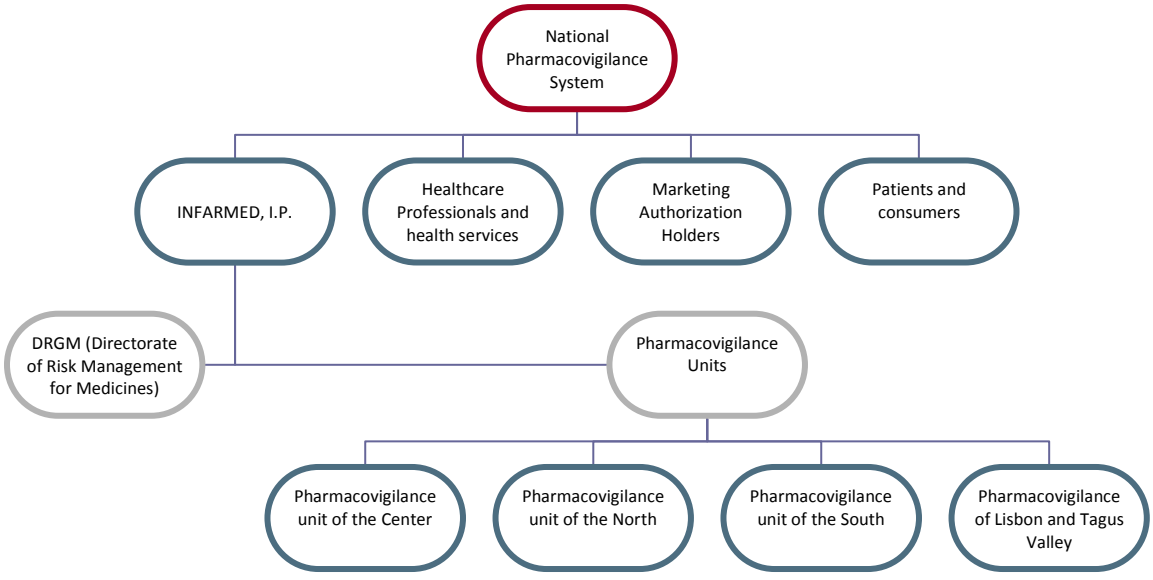



**Figure 5 -** Structure of the National Pharmacovigilance System. (58)

The national pharmacovigilance system is responsible for (35):

- Systematic collection of all information related with the risk of medicines for patients and public health, especially in what regards to adverse reactions:
    - In the human being, derived from the use of medicines in the terms of MA or outside of these terms, including overdose, misuse, abuse and medications errors;
    - Associated with occupational exposure;
- Evaluation of the safety information collected and the safety profile of medicines;
- Consideration of adequate safety measures for prevention or minimization of risks;
- Handling and processing of safety information and its communication to the other Member States;
- Adoption of the necessary regulatory measures;
- Systematic assessment of the safety profile of marketed drugs, notably by examining the relationship between risk and benefit of medicines and other relevant issues, to analyze the need to adopt safety measures;
- Participation in the preparation of technical and scientific standards for the correct use of medicines;
- Implementation of safety measures to minimize the risks associated with the use of a medicine;
- Communication and dissemination to healthcare professionals and general public, of any important information.

## 6. Developed Activities

The activities developed in DGRM are divided in two main areas**: risk management and monitoring.**

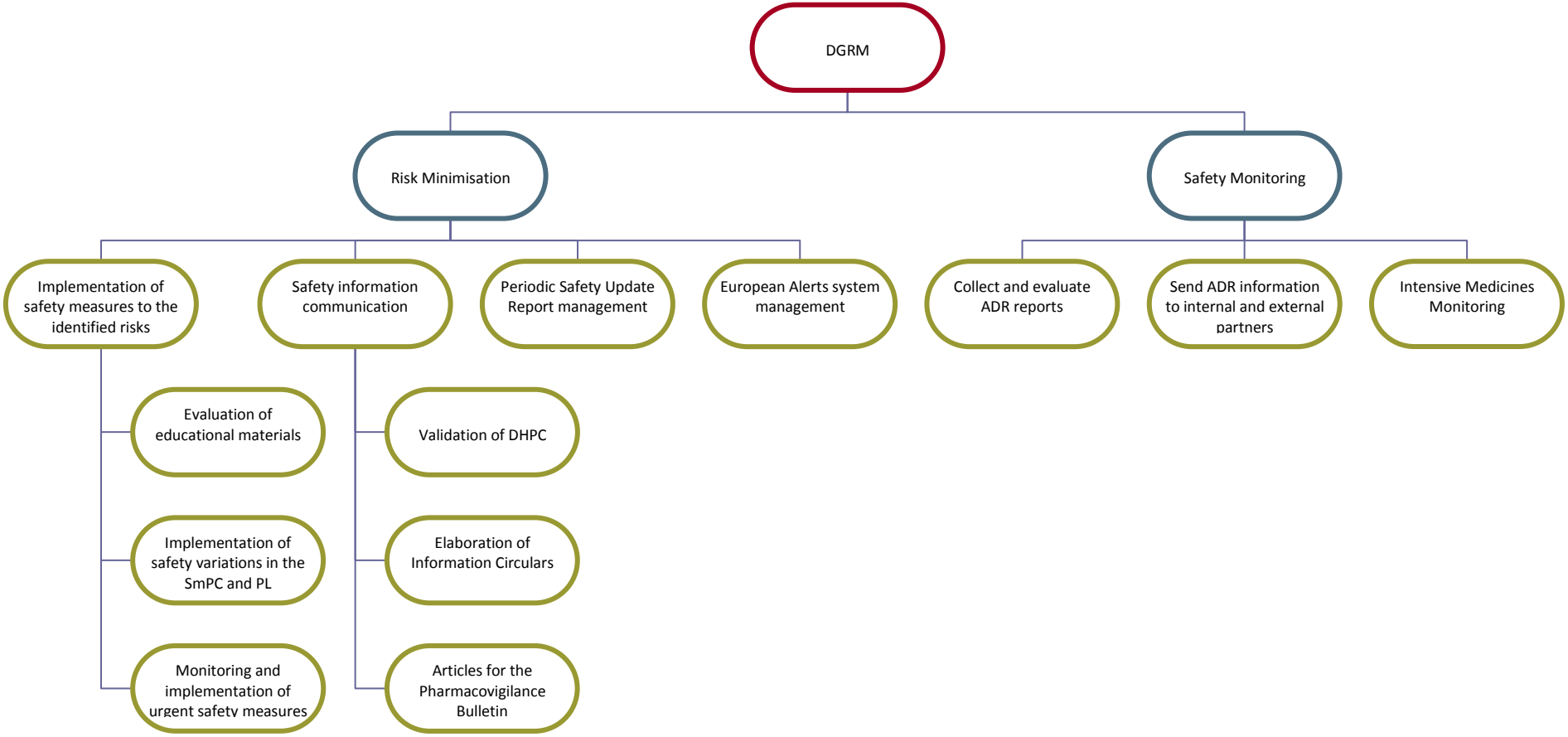
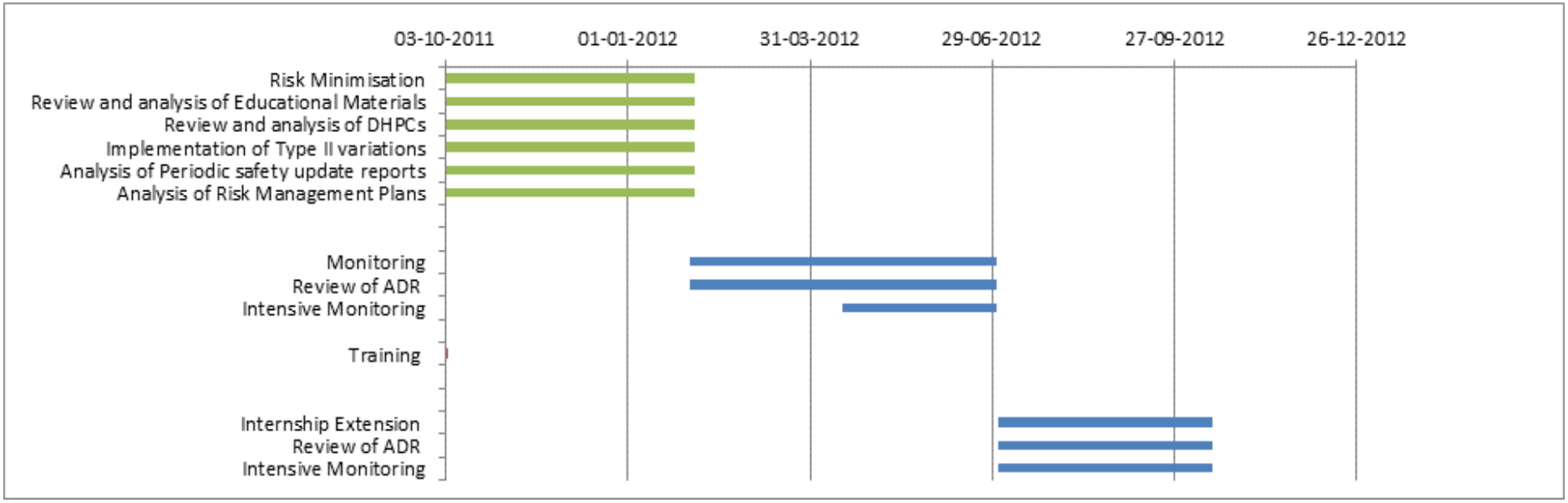



**Figure 6 - Scheme that represents the activities developed at DGRM**

## 6.1 Gant Chart




This Gant Chart represents the activities developed during my internship and the duration of each one. It is divided in 2 major groups: the first represents the risk minimization activities developed during the internship and the second one the safety monitoring of medicines. This last group of activities is also represented in the internship extension, since those were the activities developed on this period of time.

## 6.2 Risk Management System

The need for a risk management system arises from the fact that at the time of approval the safety information of a new medicine is relatively restricted. This is due to the fact that clinical trials are very small in terms of length and the amount of subjects and populations studied is very limited, which will lead to the non-detection of certain types of adverse reactions.

The main objective of this system is to ensure that the benefits of a medicine overall the risks and therefore the risk minimization activities are performed to increase the benefits or reduce the risks of medicinal product. In order to perform this, each MAH should have a risk management plan for each one of his products. (59)

In the context of risk management, competent authorities have to ensure that constant monitoring is being done and that any relevant information on medicines is transmitted to patients and healthcare professionals; ensure that any risk minimization activity is implemented and that these activities are being monitored for effectiveness; take appropriate regulatory actions to minimize the risks of the medicinal product and maximize its benefits (59)

The topic on risk management systems is discussed in the Good Pharmacovigilance Practices – Module V (Risk management systems), and main difference between the GVP module and Volume 9A is the new approach to the risks through the understanding of risk in the context of benefit (38). To achieve this, the content of risk management plan has been changed and was added new sections to analyze the overall benefit of a medicine.

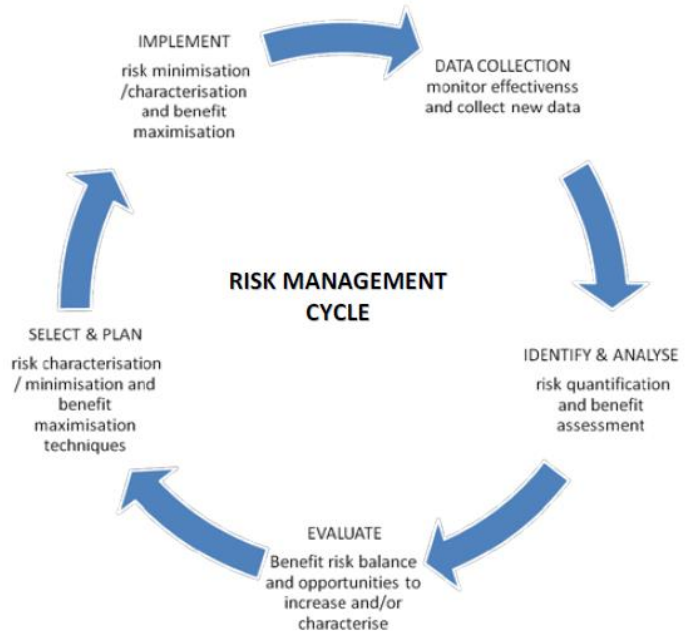



**Figure 7** - Risk Management Cycle (59)

### 6.2.1 Risk management Plan

Risk Management Plan (RMP) serves as a basis for post-authorization pharmacovigilance activities. With the new legislation, the content of a risk management plan has changed and now it also aims to analyze the effectiveness of the minimization activities. The main goals of RMP are (59):

- Identify and indicate how to further characterize the safety profile of medicinal products;
- Quantify and describe what is known and not known about the medicinal product;
- Document minimizations measures adopted to prevent or reduce the risks associated with the medicinal product and how their effectiveness will be evaluated;
- Document post-authorization obligations that have been imposed as a condition of marketing authorization;
- Document the need for studies on efficacy in post-authorization phase.

Before the new pharmacovigilance legislation came into force, a risk management plan had to be submitted in the form of an EU-RMP. An EU-RMP was not always needed to be submitted, although it may had to be submitted at any time of a product's life-cycle (38).

There are a few situations where a EU-RMP needed to be submitted (38):

- At the time of marketing authorization:
  - Any product containing a new active substance;
  - A similar biological medicinal product;
  - A generic/hybrid medicinal product where a safety concern requiring additional risk minimization activities has been identified;
- Request for a pediatric marketing authorization (PUMA);
- Any application that involves great changes in the marketing authorization (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication, including a new pediatric indication) if it is stated as needed by the competent authority;
- On the request from a Competent Authority (both pre-and post-authorization);
- On the initiative of an Applicant/Marketing Authorization Holder when they identify a safety concern with a medicinal product at any stage of its life cycle.

For some active substances that are seeking authorization via centralized procedure may be requested to submit a RMP, such as known active substances, hybrid medicinal products that suggest that additional activities are needed, bibliographical applications and fixed combination applications. (38)

With the **new pharmacovigilance legislation** the situations where a RMP is required are (59):

- All new marketing authorization applications require the submission of a RMP;
- Other situations where might be required the submission of a RMP are with an application involving a significant change to an existing marketing authorization (new dosage form; new route of administration; new manufacturing process of a biotechnologically-derived product; pediatric indication);
- Other significant change in indication, which can be a new disease area or a new age group;
- It has also to be submitted at the request by the Agency or by a Competent Authority. It should be submitted when there is any significant change in the benefit-risk balance.

**The old EU-RMP contains two parts (38):**

**Part I (38):**

- Safety Specification,
- A Pharmacovigilance Plan.

In this part, the safety profile of the medicinal product is analyzed according to the safety specification that has been identified. The safety specification is a summary of the important identified risks of a medicinal product, important potential risks, and important missing information. (38)

- **Safety Specification**

The safety specification should include the non-clinical data, in this part the safety findings that have not been adequately addressed by clinical data. It should also contain the clinical information of the medicinal product, for instance the limitations of the human safety database, populations not studied in the clinical phase, the identified or potential risks that require further characterization or evaluation. (60)

- **Pharmacovigilance Plan**

The structure and length of the pharmacovigilance plan will depend on the product that is being under analysis. This plan has the main purpose of addressing the safety concerns identified. (60)
In the beginning of the Pharmacovigilance plan a brief summary about the important identified risks, important potential risks and important missing information should be provided. In this plan, the routine pharmacovigilance activities are described. It is also provided an overview about ADR reports preparation for the competent authorities, such as expedited reports for adverse reactions and periodic safety reports; continuous monitoring of the safety profile of approved products and signal detection. (60)

However additional safety activities may be needed for medicines with important identified risks, important potential risks, or important missing information. These activities will differ according to safety specification identified. An example of one of these activities is a Pharmacoepidemiology study, to measure the incidence rate of ADRs in a different population (38). The studies that have the objective of measuring the effectiveness of risk minimization measures should be included in the pharmacovigilance plan and described with detail in the minimization plan. Examples of these studies are the drug utilization studies that measure the drug use in a specific country or by a specific population (38).

In this plan, each safety concern should have an action plan that consists in the description of the safety concern, objective of proposed action(s), the action(s) that is/are proposed, rationale for proposed action(s), milestones for evaluating and reporting. (38)

The plan should be organized according to the actions to be taken and their milestones and the actions to be completed. (38)

**Part II (38):**

- An evaluation of the need for risk minimization activities,
- If there is a need for risk minimization plan

– **Evaluation of the need for risk minimization activities**

The evaluation of the need of risk minimization activities should be provided in RMP. Some safety concerns may be adequately addressed by the proposed actions in the Pharmacovigilance Plan, however for some other risks it may not be enough due to their seriousness, and therefore risk minimization activities are needed. (38)

– **Risk minimization Plan**

This plan describes the risk minimization activities proposed for a certain safety specification, to reduce the risks associated with an individual safety concern, and it may have one or more risk minimization activities. It should be developed on a case-by-case basis.

The routine and the additional risk minimization activities should be described and the first ones are common for every medicinal product and those include (59):

- The summary of product characteristics, package leaflet and labeling
- The pack size(s) and validity
- The legal status of the product

## Impact of the new legislation in the Risk Management Plan

With the new legislation the risk management plan has a new format and new section have been added to properly assess all the issues. The new format for the RMP is already mandatory, as stated in the Implementing Regulation (EU) No 520/2012, for all new MAA. It is divided in 7 parts and the part 2 is divided in 8 modules.

As was with the old format, the risk management plan should be proportionate to the identified potential risks of the medicinal product, and the need for new post-authorization safety data.

The information contained in these sections should include enough detail so that it can be understood and important information analyzed.

**New RMP format (59):**

**Part I Product(s) overview**

**Part II Safety specification**

- **Module SI Epidemiology of the indication(s) and target population(s)**
- **Module SII Non-clinical part of the safety specification**
- **Module SIII Clinical trial exposure**
- **Module SIV Populations not studied in clinical trials**
- **Module SV Post-authorization experience**
- **Module SVI Additional EU requirements for the safety specification**
- **Module SVII Identified and potential risks**
- **Module SVIII Summary of the safety concerns**

**Part III Pharmacovigilance plan**

**Part IV Plans for post-authorization efficacy studies**

**Part V Risk minimization measures (including evaluation of the effectiveness of risk minimization measures)**

**Part VI Summary of the risk management plan**

**Part VII Annexes**

At INFARMED, the RMP analysis was important to identify if a certain medicinal product is object of risk minimization measures and what type of pharmacovigilance activities are established for it. For instance, a well-known medicinal product that doesn't have any special concerns in relation to its safety profile may only be targeted for routine pharmacovigilance activities, which are the set of activities required to fulfill the legal requirements for pharmacovigilance contained within Directive 2001/83/EC and Regulation (EC) No 726/2004. For example, a routine pharmacovigilance measure is the communication of safety information to patients and to healthcare professionals through the Patient Leaflet (PL) and the Summary of Product Characteristics (SmPC). However for some safety risks the routine measures may not be sufficient.

An additional pharmacovigilance risk management measure may be the creation of educational materials, which are evaluated for its pharmaceutical and medical precision and accuracy, at DRGM.
Through the analysis of the RMP, it is possible to ensuring the implementation of risk minimization activities at a national level, and take appropriate regulatory actions to minimize the risks of the medicinal product and maximize the benefits.

### 6.2.2 Risk Communication

The risk communication is a part of the risk minimization activities; and as previously stated, it may be a routine activity for the information contained in the SmPC and the PL. However in certain cases, when there is a safety concern that cannot be managed though this type of safety communication, the important safety information may be distributed through Direct Healthcare Professional Communications or Information Circulars and additional educational materials should be distributed to the patients, patients' families or to healthcare professionals. (38)

#### 6.2.2.1 Educational materials

An educational program is one of many additional risk minimization activities and it may be based on several types of scientific documents to ensure that the medicine is safely used. (38)
An educational material is a risk minimization activity, which is performed to reduce the risks associated with an individual safety concern. (38)
The need for educational materials will depend upon the specific safety concern and it is specified at the time of marketing authorization. As stated in the volume 9A, the aims of these activities are (38):

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

The type of educational materials will depend on the purpose and the target of these programs. It can be a physician's guide to prescribing, pharmacist's guide to dispensing; patient information brochures, checklists for both patients and healthcare professionals or specific training programs. (38)
When a medicinal product is authorized, all information about the conditions/restrictions of MAA has to be analyzed at DGRM. This is performed to identify if an educational material is foreseen. If an educational material is expected, it has to be submitted to DGRM or requested to MAH by one of DRGM's technicians. Upon receipt of this document, it is validated and analyzed by a DGRM technician. During the validation

certain aspects have to be considered, the coherence with the SmPC, the distribution universe (to whom will the material be distributed), data of dispatch and legal aspects.

The INFARMED's Advertising Team has a very important role in determining if the educational material has any content that may be transmitted as advertising to the target.

After the educational material is analyzed and all information collected, it is sent to the MAH for review, and after all revisions, it is published at Infarmed's website if allowed by the MAH.

#### 6.2.2.2 Direct Healthcare Professional Communication

A Direct Healthcare Professional Communication is defined as the information about a specific medicine that aims to ensure its safe and effective use. It is delivered directly to individual Healthcare Professionals by a MAH or by a CA. It should be submitted to DGRM, for validation, even if its content has already been agreed by EMA or by other CA. (38)

The information contained in these letters should be brought to the attention of Healthcare Professionals before to the general public. It may contain several types of information regarding suspension, withdrawal or revocation of a marketing authorisation with recall of the medicinal product from the market for safety reasons. It may also contain important changes to the SmPC, such as new contraindications, restrictions of indications, etc.). It is also used to inform that a referral procedure, which results in a significant change to the product information, was triggered for safety reasons. (38)

When there is a need to transmit, to healthcare professionals, safety information about a medicinal product, the MAH should submit a DHPC to DGRM. The role of the DRGM's technicians is to validate the letter, in terms of translation, content and to verify if the established requirements are fulfilled, such as information about the applicant and/or the MAH, the framework of the request, description of the DHPC distribution proposal (distribution universe – for whom; DHPC's distribution method – email, mail, visit, etc.) and the agreed communication plan, or the date set for distribution. It may also be submitted by EMA, the reference member state or by the EC.

The analysis of DHPCs aims to verify if it is consistent with the SmPC, and with the national applicable legislation. The message should be clear and concise, it should be objectively presented to the general public, it should also explain the reason for the distribution of the DHPC and it has to provide recommendations to healthcare professionals on how to minimize the risk.

If in the process of analysis, there were any amendments to the DHPC, these should be discussed with DGRM's Directorate, before sending it to the MAH, and only after the approval, it may be sent to the MAH. The final step of this process is to ask if the MAH authorizes the publication of the letter in INFARMED's website.

### 6.2.3 Periodic safety update report

A periodic safety update report is a pharmacovigilance document that is used to provide the benefit-risk balance of medicinal product information to the regulatory authorities, including the evaluation of this information. This document gives an update of the worldwide safety experience of a medicinal product (38). It is submitted at defined periods of time during the post-authorization phase.

The need for PSURs arises from the necessity for a continuous risk and benefits evaluation of medicinal products that are already in the market and used in everyday healthcare practice. The marketing authorization holder should prepare a single PSUR for all its medicinal products containing the same active substance with information on all authorized indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorized under different names and through separate procedures. (61)

During my internship I had the chance to analyze and validate PSURs. I was responsible for the format evaluation and to verify if there was any safety concern described in the report. Before the new legislation, the marketing authorization holder had to submit its PSUR with the format established in the Volume 9A.

The PSUR is received at DRGM, and then it is validated, to verify if it has a cover letter, a CD containing the report, the name of the MAH that is sending the PSUR and if the period covered by this report is mentioned. If all these elements are present and according with the established requirements, the report is archived or evaluated. It is evaluated by Portugal if it is the reference MS in case of a medicinal product approved through mutual recognition or decentralized procedure. In the case of a centralized product, it should be evaluated by the Rapporteur. After this evaluation, the preliminary assessment report is circulated for comments, and then the RMS or Rapporteur elaborates a final assessment report which is also disseminated for comments. This Assessment report will, if requested by the reference MS or by a concerned MS, be discussed at a PhVWP meeting. (38)

After the evaluation of a PSUR, it may be determined that is necessary to take a regulatory action, which will be communicated to MAH after an agreement with CHMP. (38)

Before July 2012, the legislation that stated the periodicity for submission of PSURs was Regulation (EC) No 726/2004 and Directive 2001/83/EC. For products authorized after 02 July 2012 (centrally authorized products) and 21 July 2012 (nationally authorized products) the MAH shall submit at 6 months intervals once the product is authorized, even if it is not marketed; once the product is marketed, 6 monthly PSURs submission should be continued following initial placing on the market in the EU and until 2 years of marketing experience in the EU, then once a year for the following 2 years and thereafter at 3-yearly intervals. (61)

The new format and content of PSURs are described in the guideline on good pharmacovigilance practices (GVP) – Module VII – Periodic Safety Update Report. There are some changes between what is described in this module and what is sated in Volume 9A relating to PSURs.

According to Volume 9A, each PSUR that arrived to DGRM, during my internship, should had the following structure (38):

The **title page** should contain the product name, the MAHs name and address, period covered by the report, the international birth date, the report date and any other identifying information at the option of MAH.

- **Executive Summary:** where the MAH should present a brief PSUR's overview to provide the reader with a description of the most important information.
- **Introduction:** where is introduced the product and place a perspective of previous reports.
- **World-wide market authorization status** (information usually provided as a table):
    - Dates of marketing authorization and renewal;
    - Any qualifications surrounding the authorization;
    - Treatment indications and special populations covered by the marketing authorization;
    - Lack of approval, with an explanation by the regulatory authorities;
    - Withdrawal by the company of a license application submission if related to safety or efficacy;
    - Dates of launch in each country when known;
    - Dates when the marketing authorization has been revoked/withdraw or suspended by a RA or voluntarily by the MAH;
    - Invented name(s).
- **Update of Regulatory Authority or MAH Actions Taken for safety reasons** - in this section the actions taken by the regulatory authorities or by the MAH are described. These actions include:
    - Marketing authorization withdrawal or suspension
    - Failure to obtain a marketing authorization renewal
    - Restrictions on distribution
    - Clinical trial suspension
    - Dosage modification
    - Changes in target population or indications
    - Changes in the formulation
    - Urgent safety restrictions
- **Changes in the reference safety information**: In this section, any change in the company core safety information (CCSI), made during the period covered by the report, should be clearly described.
- **Patient exposure**: an estimation of patient exposure to the medicine and the method used to estimate that exposure should be provided. If it's not possible to estimate the number of patients then other measures of exposure, such numbers of prescriptions, number of dosage units or patient-days are considered acceptable.

- **Presentation of Individual Case Histories**: In this section the cases are presented as line listings. In this list must be included:
    - All serious reactions; and no-serious unlisted reactions, from spontaneous notifications;
    - All serious reactions (attributable to drug by either investigator or sponsor), available from studies or named-patient ("compassionate") use;
    - All serious reactions, and non-serious unlisted reactions, from the literature;
    - All serious reactions from regulatory authorities.
- **Line-listings:**
    - All serious adverse reactions and non-serious unlisted adverse reactions from spontaneous reporting;
    - All serious adverse reactions available form post-authorization safety studies and other studies or named/compassionate use;
    - All serious adverse reactions, and non-serious unlisted adverse reactions from the literature;
    - All serious adverse reactions transmitted to the Marketing Authorization Holder by worldwide regulatory authorities.
- **Summary tabulation**: For each line listings there is a summary tabulation, usually it is separated for serious reactions and for non-serious reactions, for listed and unlisted reactions.
- **MAH's Analysis of Individual Case Histories**: The MAH may want to comment an individual case, to discuss any safety concern.
- **Studies**: In this section, the MAH should describe the studies where any safety information was collected and with potential impact for the safety profile of the medicine. It may contain completed studies, studies specifically planned or in progress, and they may be non-clinical, clinical and epidemiological studies. Examples:
    - Newly analyzed company-sponsored studies;
    - Targeted new safety studies planned, initiated or continuing during the reporting period;
    - Published safety studies.
- **Other Information:** it may contain Efficacy-Related Information, where a lack of efficacy may represent a serious threat to the treated population. It may also contain Late-Breaking Information, which represents important information received after the data lock point. **Overall Safety Evaluation:** In this section there should be an Overall Safety Evaluation, where the MAH evaluates the safety information collected during the period of the report. Concise analysis of the data presented and assessment of the data collected during the period.
- **Conclusion:** It should indicate which information does not fit the previous cumulative experience and specify and justify any action recommended or initiated. Most important, this section should address the overall risk-benefit balance in the context of the data presented in the PSUR and

indicate which data and results are not in accordance with the previous cumulative experience, it should also specify and justify any safety action recommended or initiated.

**New legislation – the impact in Periodic Reporting**

With the new legislation the format and content of these reports have been changed. Nevertheless, until January 2013 it was possible to submit periodic reports with the new or with the old format.
Since all suspected adverse reaction data is directly summited to Eudravigilance database, the scope of PSUR has changed to an analysis of the risk-benefit balance of a medicine rather than just a list of all individual case safety reports that are already submitted to Eudravigilance, avoiding this way the duplication of efforts. Therefore the main goal of PSUR, as stated in Directive 2010/84/EC, is to make a comprehensive and critical analysis of the risk-benefit balance of the medicinal product taking into account new or emerging information on the context of cumulative information on risks and benefits (61). Therefore PSURs should be linked to the risk management system for newly authorized medicinal products and these should be proportional to the risks posed by medicinal products. The routine reporting won't be necessary for generic medicinal products, for medicinal products containing an active substance for which well-established medicinal use has been demonstrated under the Directive 2001/83/EC, for homeopathic medicinal products and for traditional-use registered medicinal products (31). However at the request of a competent authority, the MAH should submit a periodic safety reporting for products that don't require the submission of these reports, due to concerns relating to pharmacovigilance data or lack of safety information. (31)
To avoid duplication of effort and optimize the resources used in the evaluation of PSURs, the data lock point and frequency of submission of these reports, for different medicinal products containing the same active substance or combination of active substances has been harmonized to allow a single assessment of PSURs in the EU, for centralized and nationally approved medicinal products, in more than one MS (61). This single assessment allows the evaluation of all available safety data on the benefits and risks of an active substance or combination of substances.
A list of the reference dates and frequency of submission of PSURs is already available, it contains the harmonized data lock point for PSURs with the same active substance and combination of substances (61).

**New structure of PSUR**

The required format and content of PSURs in the EU are based on those for the Periodic Benefit Risk Evaluation Report (61).
The new format has 3 Parts: the first one is the title page, the second the executive summary and the third is the table of contents. In this last part, the information about the safety profile and all relevant

information about the clinical trials performed after the product authorization for another indication or population is described. It is also important to provide data summaries on the benefits and risks of the medicinal product.

### 6.2.4 Safety Variations (Type II safety variations) and urgent safety restrictions

Once a marketing authorization has been granted for a Medicinal Product, safety signals may arise which might have a serious impact on Public Health. Depending on the nature of the risk and the impact in Public Health, a range of regulatory actions can be taken.

Among the regulatory actions that can be engaged, it is possible to introduce provisional changes to the product information through an urgent 24 hour ”Urgent Safety Restriction procedure”, in order to restrict the use or to introduce warnings or precautions for the safe use of the medicinal product. This regulatory action may be started by the MAH on its own initiative or by the regulatory authorities and, in the case of centralized marketing authorizations, the Commission. (62)

A document containing the plan on the safety concerns identified is circulated through the EU National Competent Authorities for comments and then decided centrally at the European Commission (63).

Types of variations in medicinal product authorization information:

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

The minor variations of type IA and IB do not represent any safety concern, those are not analyzed and approved in DGRM, and therefore are not in the scope of the present document.

A major safety variation is contained in the group of type II variation; it does not represent an extension and it has a significant impact on the Quality, Safety or Efficacy of a medicinal product. At DRGM, the variations analyzed are exclusively for safety concerns, and those usually reflect major changes in the safety profile of a medicinal product. The safety type II variations are a safety measure that provides an update to the information contained on the SmPC and PL for medicinal products for which a potential safety issue has been identified (62). To this end, Infarmed and more precisely DGRM notify the MAHs of these medicinal products by letter to submit the respective application for a Type II Safety Variation. The communication between DGRM and each MAH and the submission of the necessary documents is done through the electronic submission program for Type II Safety variations requested by Infarmed for the medicinal products for which MA was obtained by national procedure.

However certain changes to a marketing authorization that fundamentally alter the terms of this marketing authorization cannot be granted following a variation procedure, and therefore have to be submitted as an

extension application. These changes are to be submitted as an extension application and are listed in Annex I of the Variations Regulation. (64) (62)

The following situations, listed in Annex I, are the main categories of changes requiring an extension application:

- changes to the active substance(s);
- changes to the strength, pharmaceutical form and route of administration;
- other changes specific to veterinary medicinal products to be administered to food-producing animals or change or addition of target species.

The deadlines for the submission and evaluation of the safety variations will depend on the urgency and potential public health impact of the safety issue. Therefore, the CA should establish deadlines that are suitable for that matter, and will liaise with Marketing Authorization Holders regarding the appropriate deadline, as required. Failure of Marketing Authorization Holders to submit the variation application within the deadline may be considered as non-compliance. (65)

#### 6.2.5 Rapid alert and Non-urgent information system

The CA and the Agency have a communication system to exchange information. To support rapid notification of safety concerns and therefore take appropriate action towards the minimization or resolution of a certain issue, the CA, the Agency and the EC operate a Rapid Alert (RA) and Non-urgent Information System (NUI). This type of communication system may be initiated by one of the Competent Authorities of Member States or by the Agency. (38)

The pharmacovigilance data related to medicinal products that must be shared with urgency should be transmitted through a Rapid Alert between the CA, the Agency and the EC. The information transmitted with this level of urgency indicates that action may be needed urgently in order to protect public health. (38)

A RA should be used when a MS or the Agency has a safety concern that has a major impact on the known risk-benefit balance of a medicinal product and it considers that prompt action should be taken and that it should be communicated to the Healthcare Professionals/the general public (38). Responses to an RA should compiled by the initiator and then sent to all Member States, the Agency, the EC and to the Rapporteur in case of a centralized product, no later than one week after the receipt of the RA, unless otherwise specified (38). According with volume 9A, this information usually refers to:

- A urgent safety restriction, suspension, revocation or withdrawal of the marketing authorization, recall or the suspension of marketing and/or use of a medicinal product;

- Action for human blood- and plasma-derived medicinal products following occurrence of vCJD (variant Creutzfeldt-Jackob disease) in a blood donor (with specification of batches on the market as well as expired batches);
- Important changes in the SmPC:
    - Introduction of new contraindications;
    - Introduction of new warnings;
    - Reduction in the recommended dose;
    - Restriction of the indications;
    - Restrictions in the availability of a medicinal product;
- Need to inform Healthcare Professionals or Patients about an identified risk without delay.

It can be send in other situations such if the reporting rate of certain expected serious reaction increases or suggest greater severity. (38)

If the information does not fit the criteria for a RA, then NUI should be used. Usually it is used to exchange emerging pharmacovigilance information at an early stage, such as a new safety signal or an update status of a regulatory action, or just a request for information. (38)

The timeline for response to a NUI is established by the initiator which is also responsible for the compilation of all responses and circulation of this information to all MS, the EC and the Agency. (38)

At DGRM, the NUIs are received and then distributed according with the medicinal product's CFT (*classificação farmacoterapêutica)*. The majority of NUIs are sent by other regulatory authorities or by the Agency. The information is collected, organized and then analyzed by the DGRM's director to be sent to the initiator.

The process may be started by Portugal, if there's a detection of a safety signal or any safety concern that requires an urgent measure, towards a medicinal product or group of substances, such as suspension or revocation of a marketing authorization. The document which contains an explanation of the safety concern is inserted in EPITT and then sent through the All Human RA email list to all MS, the Agency and EC. If the document requires a reply, then the DGRM has to receive and compile every response into a single document, which after Directorate validation has to be inserted into EPITT. The subject under debate in the NUI or RA has to be discussed in the PRAC, to assess if any measures are necessary to protect the public health.

## 6.3 Safety Monitoring of Medicines

As stated in the legislation each Member State should have a system for the collection of spontaneous suspected adverse reaction from healthcare professionals, and since July 2012 also from patients/consumers, although it was already possible but only with a medical confirmation. (66)

With the new legislation (July 2012) the definition of adverse reaction changed, and now it covers more scenarios for the event of an AR. According to the Directive 2010/84/EC, the definition of adverse reaction is a response to a medicinal product that is noxious and unintended and it includes the use of the medicine within the terms of the marketing authorization and also outside the terms of marketing authorization, which includes overdose, off-label use, misuse, and abuse and medication errors. Occupational is also considered as an adverse reaction and it refers to the exposure to a medicinal product as a result of one's professional or non-professional occupation. (66)

A suspected adverse drug reaction may be reported by a healthcare professional by various ways, such as writing, by telephone, or electronically. Healthcare professionals may report directly to DRGM or to the Regional Units and directly to MAH. When a reporter notifies on its own initiative, it is called a spontaneous report and it is an unsolicited communication by a healthcare professional or by a consumer to a competent authority or to a MAH. (66)

On the other hand a notification may also be solicited, and it is called solicited report, these are derived from organized data collection systems, which may be clinical studies, non-interventional studies, post-approval named-patient programs, registries, surveys or compassionate use. (66)

A report that arises from worldwide literature may be a spontaneous one or it may result from a non-interventional study, nevertheless the medical and scientific literature is a source of safety information about the medicinal product that allows marketing authorization holders and competent authorities to monitor the safety profile of a medicine and calculate its benefit/risk balance. Therefore MAHs should perform a systemic literature review of widely used reference databases, no less than once a week. However there are a few situations where a MAH does not have to report a literature case as an ICSR if another company's brand is explicitly the suspected medicinal product in the article, or if the adverse reaction occurred in a country where the MAH doesn't have a marketing authorization or has but it's not commercialized. (66)

It is important to verify if all the necessary elements are present, since the notification has to have minimum information to be considered valid. Therefore the report should include at least one identifiable reporter, one single identifiable patient, one or more reaction /event and one or more suspected drug(s). The patient may be identified by initials, patient number, and date of birth, age, age group, or sex. The reporter (primary source) may be identified by name or initials, address or qualification. It is also important that any contact detail is available. It is also mandatory the notification has at least one suspected active substance/medicinal product and at least one suspected adverse reaction. In the absence of one of these

four elements the ICSR is considered invalid and it should be reported, however efforts must be made to obtain the missing information, nevertheless, the marketing authorization holder should keep these cases in its database. (67)

All the serious adverse reactions, even if they are already described should be reported by MAH within 15 days from the receipt of the information containing the minimum criteria for reporting an ICSR. The criteria for seriousness are (67):

- Death
- Life threatening
- Involved or prolonged inpatient hospitalization
- Involved persistence or significant disability or incapacity
- Congenital abnormality
- Other (medically significant)

Besides the serious reactions, also the non-serious should be reported within the period of 90 days from the receipt of minimum information for reporting (66)

There are also several rules for reporting in special situations:

- **Use of a medicinal product during pregnancy or breastfeeding:** these cases should be followed during the pregnancy and after, during the development of the child. Not all exposures during pregnancy should be reported to competent authorities as ICSR, when the pregnancy has a normal outcome, without future consequences for the child, it should only be described in the periodic safety report(66). However, these cases have to be reported, if the MAH stated it in the risk management plan or if the DGRM demands so. (66)
- **Use of the product in a pediatric population:** in this case, when a medicinal product is used by this population is important that the company keeps all the records about the case including follow-ups to describe in the periodic safety report, however if no ADR occurred then it does not qualify for ICSR and it should not be reported to the DGRM or to Eudravigilance. (66)
- **Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure:** if no adverse reaction occurred in these situations, then those should not be reported to the DGRM, however those should be described in the periodic safety report. However, in the case of a serious safety issue that has impact in the benefit-risk balance of the medicinal product, it should be notified to DGRM. (66)
- **Lack of therapeutic efficacy:** lack of therapeutic efficacy normally should not be reported, but when a lack of efficacy is verified with medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines and contraceptives, it should be reported on an expedited manner, within 15 days after the receipt of the information on the case. (66)

When one of the previously described reports arrives at DRGM, if the only adverse reaction codified is incorrect use or other code that describes the use outside the terms of marketing authorization, a pharmacovigilance technician send an *information request* (via email) to the marketing authorization holder to nullify the case in its database.

### 6.3.1 Electronic transmission

Most of ICSR are sent electronically to DGRM by the MAH. The mandatory status for electronic transmission of ICSR was stated in the Regulation No. 726/2004 and Directive 2001/83/EC. The data elements for transmission of ICSR are described in the ICH guideline E2B: Data Elements for transmission of individual case safety reports. In electronic transmission, each case has specific number that identifies it, a WWID (worldwide identifier). In electronic transmission the WWID is the case number, this is a unique number that is the same for follow-ups of a single case. This belongs to the section: A. Administrative and Identification Information, along with the primary source(s) of information and information on the sender and receiver of the case safety report. Besides the administrative information, there is another section: B. Information on the case, which has the patient characteristics, reaction(s)/event(s), results of tests and procedures relevant to the investigation of the patient, drug(s) information and narrative case summary and further information. This guideline states what should be present in each section and how each field should be filled. Each section is identified by a letter, followed by numbers, such as follows: A.1.10.1. (68)
What is evaluated in each sections and how each should be filled is discuss ahead in this chapter.

### 6.3.2 DGRM ADR database – SVIG

DGRM has a database for the management and storage of ADRs called SVIG and it allows the electronic reception or manual insertion of cases.
Each section of this database is based on the E2B ICH Guideline. The SVIG sections (most important sections for the validation and quality of the case) are:

- **Administrative information**: contains the WWID number, the safety number and the Infarmed's number. It also contains the dates of the initial and most recent reception of information by the primary source and in the sector. It also contains the type of report (spontaneous, study or another), the country where the adverse relation occurred, the country of the reporter, the information if the case received medical confirmation and the seriousness of the case, including the seriousness criteria.
- **Annexes**: In this section the documents that accompanied the notification are attached and the list of similar cases and duplicate cases is also constructed.
- **Sender**: The information about the sender is described in this section, such as the type of sender (pharmaceutical company, CA, health professional, etc.). The sender's identity, name and address

are also presented in this section. Usually the sender is the secondary source, which received the information about the case from the primary sender, the reporter.

- **Reporter (primary source):** The reporter is the person that collects and sends all the information about the case directly to DGRM, regional units or to the marketing authorization holder. A reporter may be identified by the name or initials, the address or the country. The qualification is a mandatory section for electronic transmission; among the options are physician, nurse, pharmacist, other healthcare professional, lawyer, consumer, etc.
- **Case data**: The case data contains information about the patient, such as the name initials, the age, date of birth, weigh, height, gender, etc. In another section it contains the clinical history, which should be used to list all procedures and medical conditions that begun before the adverse reaction. These medical conditions may be chronic and present at the time of the adverse reaction. The pharmacological history is also present in this section and it should be filled with the information about the medicinal products that the patient used during a certain period of time before the adverse reaction. The final part of the case data are the tests performed to the patient, those are performed at the time of the adverse event or after, as follow up measure.
- **Patient Death:** This section is only filled if the patient died; it contains the date and the cause of death.
- **Parent information:** This is used for a parent-child/fetus report, where the parent had no reaction/event. It contains the clinical and pharmacological information about the parent.
- **ADR information:** This contains all the information about the adverse reaction(s), including the information about the dates and duration of the adverse reaction. All adverse reactions should be reported in MedDRA.
- **Suspected medicinal product(s) information:** The suspected medicinal products are listed in this section, and it contains information of the treatment dates, the medicinal product's allotment, measure taken towards the medicinal product (dose augmentation, unknown, unchanged dose, not applicable, dose reduction and drug suspension), it also contains the result of the re-exposition to the medicinal product.
- **Narrative**: The case is described with all the details in this section and it is written in a text manner. The follow-up information is also contained in this section with the identification of it and the date it was received by the company.

### 6.3.3 Reception, validation and management of all notification sent by MAH

Before its submission to DGRM and in order to ensure that the minimum information required is included in the report, the MAH is expected to validate all adverse reactions reported. However even with the cases'

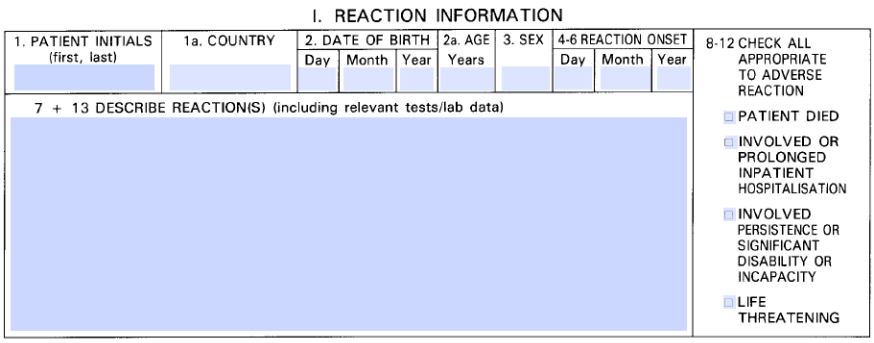
validation by the marketing authorization holder, the pharmacovigilance technicians of DRGM also validate all the expedited cases that arrive through CIOMS I or electronically.

When a MAH receives a spontaneous report of an ADR, that qualifies for an expedited report, from a healthcare professional or other source, it should be reported to DGRM. It is also possible that a healthcare professional reports a reaction directly to the competent authorities. If the MAH becomes aware of this situation, he should report the case and inform the DGRM that it is a duplicate.

It is also possible to monitor for ADRs through organized data collection systems, such as post-authorization studies, patient registries, surveys of patients or healthcare providers, etc.

The transmission of these adverse reactions is done electronically, save in exceptional circumstances, for all authorized medicinal products in the EU. However, if a MAH is not already in electronic transmission or if it is not possible to send a notification electronically then, the report may be send in CIOMS I format in the case of serious reactions, or CIOMS II, in the case of a non-serious reaction. The CIOMS I form has been a widely accepted standard for expedited adverse event reporting. Usually only CIOMS I is received since the most important notification are the ones that refer to serious reactions and/or non-described. This may be send to DRGM by email, fax or post-mail, with the same reporting timelines.

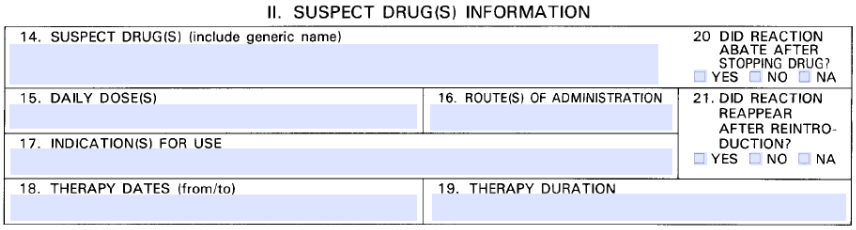
The CIOMS I (69) is divided into 4 groups: the first one refers to the reaction information. It contains the information that identifies the patient, the description of the reaction, with the codification of which reaction in MedDRA, the criteria for seriousness and the narrative, in which the event is described with detail.


I. REACTION INFORMATION

| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | | | 2a. AGE | 3. SEX | 4-6 REACTION ONSET | | | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Day | Month | Year | Years | | Day | Month | Year | PATIENT DIED |
| | | | | | | | | | | INVOLVED OR PROLONGED INPATIENT HOSPITALISATION |
| | | | | | | | | | | INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY |
| | | | | | | | | | | LIFE THREATENING |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) | | | | | | | | | | |

**Figure 8 -** CIOMS I form, section I Reaction Information.

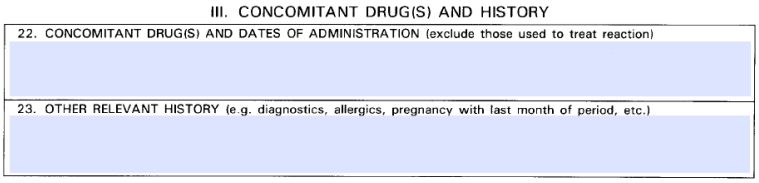
The second section contains the suspected drug(s) information, where the name of the drug is present (brand name or, when not possible to obtain this information, the active substance), posology and the result of de-challenge and re-challenge.


II. SUSPECT DRUG(S) INFORMATION

| | | |
|---|---|---|
| 14. SUSPECT DRUG(S) (include generic name) | | 20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA |
| 15. DAILY DOSE(S) | 16. ROUTE(S) OF ADMINISTRATION | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA |
| 17. INDICATION(S) FOR USE | | |
| 18. THERAPY DATES (from/to) | 19. THERAPY DURATION | |

**Figure 9 -** CIOMS I form, section II Suspected drug information.

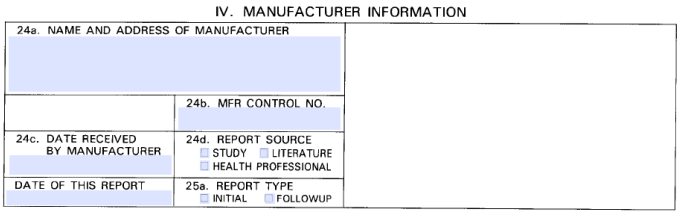
The section III describes the concomitant drug therapy (drug(s) that was/were being concomitantly administrated with the suspected drug) and the clinical history, which includes all the medical procedures and history of diseases that had or has but are not a result of an adverse reaction to the product.


III. CONCOMITANT DRUG(S) AND HISTORY

| |
|---|
| 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) |
| 23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.) |

**Figure 10 -** CIOMS I form, section III concomitant drug(s) and history.

Finally, the IV section is used to add information about the manufacturer; it is many times the same person that sent the case to DGRM, it also contains the date in which the manufacturer received the information about the case and the date in which the report is finished. The source or the origin of the report is identified, and it can be a literature report, spontaneous or a study. The report type is also selected between initial or follow up. There are marketing authorization holders that in this section also give information about the primary source (reporter) of the report.


IV. MANUFACTURER INFORMATION

| | | |
|---|---|---|
| 24a. NAME AND ADDRESS OF MANUFACTURER | | |
| | 24b. MFR CONTROL NO. | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL | |
| DATE OF THIS REPORT | 25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP | |

**Figure 11 -** CIOMS I form, section IV manufacturer information.

When a case is received through a CIOMS I form, it has to be manually inserted into SVIG. This database generates a number, that is the same in case of follow up, and thus the new information is inserted in the same case.

In the case of electronic transmission, it may be in two ways, from the MAH database and/or from DRGM to MAH. The MAH inserts the information into his database then it is transmitted via XML and sent to SVIG. An

acknowledgement report is generated from this operation to inform the MAH that the information was well received, received with an error or non-received.

As described previously, after the arrival of the case, there's the *validation step*, which consists in the verification of the administrative and minimum information with the aim to verify if it is present and properly filled.

If the minimum criteria is not present, then a solicitation of information to the MAH should be performed, to whom is given a specific date to send the information. This request is also made for another type of information, to enhance the quality of the notification and to simplify the signal detection. When the requested information arrives, it is verified again. If the information is in accordance with the requirements, then a duplicate search is made and it is registered as a new case, a follow-up or a duplicate. A duplicate search is made in SVIG, and it is made using the patient initials, age, date of birth, adverse reactions and/or by suspected drug. This search is due to the fact that some ICSRs, especially those which are serious, may be reported to DGRM from more than one source, such as the MAH or a healthcare professional. Each duplicate should be market as inactive, and the case that is not a duplicate should remain active.

Each case may receive various follow-ups, these are sent when new important information about the case is obtained and it is important for its scientific evaluation. When a new case is received and has the same WWID of another case, it means that this is a follow-up of a previous case and therefore, to the initial case is added new information. It is important to verify if the dates are correct, since the section with the most recent date of reception has to be different from the date of initial reception of the case by the company and by the sector. When a follow-up is received through CIOMS I form, in order to identify the initial case of the follow-up, a brief verification and comparison of the data between the two cases should be performed.

There are three scenarios that must be considered when managing case reports and duplicates. The first scenario is two duplicated cases that were directly reported to DGRM by healthcare professionals - in this situation the case that should be market as the inactive is the one that has a posterior date of reception in the sector. All the relevant information in the inactive case should be added to the active case.

In the scenario of a case that was sent a healthcare professional and a MAH, the active case is the one that was sent by the healthcare professional and the other case, sent by the MAH is inactivated. All the relevant information in the case sent by a marketing authorization holder should be added to the active case.

When the same case is sent by two marketing authorization holders, the active case is the one that has the oldest date of reception in the sector and the other should be inactivated.

After these procedures a *technical analysis* of the case should be performed.

**Technical validation of the cases**

After the validation of the ICSR, the pharmacovigilance technician analyzes the information contained in SVIG. It has to be kept in mind that is not necessary to fill every data element of every section, since it is

almost impossible to do, but it is necessary to fill the minimum data elements so that the report can be electronically transmitted and validated.

**Analysis of each section of the ICSR**

**Administrative section (E2B A.1)**

The analysis starts with the verification of the WWID and the safety ID, in order to verify if those are well constructed. It also important to verify the reception dates.

In SVIG database there are four data fields that have to be filled so the case can be validated:

- Date of initial reception by the company
- Date of the initial reception in the sector
- Date of most recent reception by the company
- Date of the most recent reception in the sector

For an initial case:

- Date of initial reception by the company is the same as the date of most recent reception by the company;
- Date of the initial reception in the sector is the same as the date of the most recent reception in the sector.

In the case of a non-valid ICSR, the “Date of initial reception by the company” should be the date of receipt of the initial non-valid ICSR, although it can only be reported when containing the minimum criteria, therefore the element data “Date of the initial reception in the sector” is the same as “Date of the most recent reception in the sector”.

For a Follow-up case:

- Date of initial reception by the company is previous to the date of most recent reception by the company;
- Date of the initial reception in the sector is previous to the Date of the most recent reception in the sector.

The data element “type of report” (E2B A.1.4) is also listed in the administrative section, it can be spontaneous, if the case arises from a spontaneous observation, it can be defined as a study, if it arises from an observational study or it may be codified as other, if it arises from a literature report and it is

unclear if it arises from a spontaneous observation or from a study (68). This is an E2B field and it is very important to be correct, if not, then an information request should be send to the MAH to correct it.

Another E2B data element is the reporter country (E2B A.1.1), this is the basis for the construction of the WWID, in other words, the reporter country sets the first part of the WWID code, for example, when the reporter is form Portugal, then the WWID will begin with PT.

When a report is nullified, it is presented in the A.1.13 data element - report nullification. This item should be used to indicate that a previously transmitted report should be considered completely void. An explanation for the nullification should be provided and only the sender can nullify the case, and once it has been nullified, it cannot be reactivated. This is used when a case has been identified as a duplicate of another individual case, previously submitted by the same organization. (68)

When a wrong WWI was accidently used and does not refer to an existing case, it should be nullified and other case with the correct WWID should be send. However if the WWID refers to an existing case, the report should not be nullified but rather the marketing authorization should submit a follow up to correct the information previously sent. A new ICSR should be created and submitted with the correct WWID. (68)

A case should also be nullified when certain elements are not consistent, for instance, when the patient took the suspected medicinal product after the reaction onset or did not took the medicinal product at all. It also qualifies for nullification if the reporter confirms that the adverse reaction did not occur to the patient or there is no valid patient for the individual case (66).In these cases the minimum criteria for reporting is no longer met and therefore the case is not an ICSR.

In the section of administrative information, it also important to verify if the case is serious and the criteria for seriousness (death, life threatening, hospitalization, persistent or significant incapacity, congenital anomaly/birth defect or other medically important condition) (67).

If the case resulted in death then the section “patient death” should be filled if there is any information regarding the cause of death and the results of the autopsy and in this report, at least one reaction should have the outcome death (70).

**Annexes section**

The WWID of each duplicate or related case should be listed in the annexes section and in the case of the duplicate cases, each one of these should have the WWID of the active case in the section for the authority comments.

**Sender section**

This section contains the information about the case sender that may not be the MAH, but someone responsible for the electronic transmission.

The type of sender (ex: pharmaceutical company, regulatory authority or healthcare professional) has to be filled so the case can be validated (68).

**Reporter section**

First it is important to verify which type of reporter reported the case or in other words the reporter's qualification (physician, pharmacist, dentist, other healthcare professional, consumer, lawyer or other non-healthcare professional) (68).

In the case of a literature report, the literature reference (E2B A.2.2) must be filled according to Vancouver guidelines (66).

If in the "administrative section", the type of report is study, then in the "reporter section" other studies or individual patient use programs should be selected, if clinical trial is selected, then the case should not be analyzed and validated by DGRM, since SUSAR's are under the responsibility of another directorate at INFARMED. The name of the study should be filled (E2B A.2.3.1).

**Case data**

In the "section case data" there are four sub-sections: patient characteristics, relevant medical history, relevant past drug history and the tests performed to the patient.

**Sub-section: patient characteristics**

One of the following data elements have to be filled in order to consider the report valid (68):

- Patient initials, for privacy agreements, this data element may be filled with "privacy" instead of the patient's initials, or with nothing, when the initials are unknown;
- The patient gender;
- Date of birth, age, or age group of the patient.

If none of these elements are filled then an information request has to be sent to the MAH, and if he does not have information about any of these elements then the case has to be nullified since it has not the minimum criteria for reporting.

In the case of a fetal demise or early spontaneous abortion, only a parent report is applicable, however if both parent and the child/fetus had an adverse event, then two reports should be prepared and linked by using the related cases sub-section in each of the reports. When only the child/fetus had an adverse reaction, the information provided in this sub-section applies to the child/fetus and characteristics concerning the parent, who was the source of exposure to the drug, should be provided in section Progenitor information. This is a parent-child/fetus report and if only the parent had an adverse reaction, then only one report should be submitted, with the information about the mother and the gestation time. When the reaction(s) occurs in the fetus, the data element "Gestation period when reaction/event was observed in the fetus" should be used. (68) (66)

If the patient (child/fetus) and parent sections are not properly filled with the right information, an information request should be sent the marketing authorization holder requesting to correct the data elements and send a follow up. (68) (66)

Besides the data elements described for this sub-section, there is also other information that can be provided to improve the quality of the case and facilitate its analysis, and those are the patient height, weight and last menstrual period date. (68) (66)

**Sub-section relevant clinical history**

This section may or may not be filled with the patient clinical history; however if it is described in the narrative then it should be listed in this section. It contains all the previous medical conditions and procedures; it should also include any current health condition that has started previously to the adverse reaction. (68)

The data elements listed in this sub-section have to be provided according to the last version of the MedDRA terms.

**Sub-section relevant past drug history**

This section should only include medication previously taken and not those taken concomitantly or that may be involved, or are potentially involved in the current adverse reaction(s) event(s). (68)

**Tests performed to the patient**

All the tests performed to the patient should be listed in this section and coded in MedDRA. (68)

**Patient Death**

This section should only be filled if the patient died, therefore the seriousness criteria and the outcome of at least one of the adverse reactions should be death, in order to validated the case (68), (70).

The information about the date of death (E2B B.1.9.1) and/or cause of death (E2B B.1.9.2) should be present (68). If an autopsy was performed and the cause of death was determined, it can be referred in this section.

**Parent information**

This section should only be filled if the report is a parent-child/fetus report (the parent had no adverse reaction(s)) and it should contain the parent data, such as the parent's age, parent's birth date or parent's gender. This section should be used in the case of a parent-child/fetus report where the parent had no reaction/event. It can also contain the height, weight or the last menstrual period date of the parent. (68)

**ADR information**

This section should contain at least one valid adverse reaction with the correspondent outcome. The outcome can be chosen between the following: recovered/resolved; recovering/resolving; not recovered/not resolved; recovered/resolved with sequel; fatal or unknown. The outcome must be in

accordance with what is described in the narrative and with the seriousness criteria. It is also important to verify the date of adverse reaction onset to confirm that it happen after the intake of the suspected medicinal product. (68)

Only the MedDRA Lowest Level Term (LLT) most closely corresponding to the reaction/event as reported by the primary source should be provided (68).

During the reaction codification the MedDRA Term Selection: points to consider (bases on the last version) should be consulted and analyzed. It contains guidance on how to codify each adverse reaction in each situation.

There are a few situations that are quite common during the codification of an adverse reaction. For example death can only be codified as an adverse reaction if there is no other adverse reaction or information of what caused death to the patient.

When the primary source reports the definitive diagnosis along with the symptoms of that diagnosis, the preferred term to codify is the definitive diagnosis. When a provisory diagnosis is given with the symptoms, then all of these terms should be codified and reported. (70)

When lack of efficacy is reported, it is important to code the terms “lack of effect” and although it is not always an adverse reaction, it is important to record modification of effect (e.g. increased, prolonged) (70).

There are also a few situations that are not to be reported, however some marketing authorization holders report those due to intern arrangements and company policies. For instance, the use of a medicinal product during pregnancy without any adverse reaction does not qualify for reporting, however in the event of reporting then it should be coded as pregnancy and no adverse effect. (70)

There are many other situations that require special attention in order to improve the quality of the cases and the constant enhancement of the national pharmacovigilance system.

**Suspected medicinal product(s) information**

In this section there is a list of the suspected and concomitant medicinal products and the involvement of them in the adverse reaction. The characterization of the involvement of the drug may be: suspected, concomitant or interacting (68).

The medicinal products may be identified by proprietary medicinal product name, active substance or DCI (*Denominação Comum Internacional*). When possible a medicinal product should always be coded with the brand name. It is very important to verify what type of drug it is and how is it coded. If it is wrongly codified then an information request should be sent to MAH in order to correct it.

The therapeutic class of the medicinal product should not be used to codify a medical product, for example, when Anti-Histaminic is reported as a suspected medicinal product, then it should be correct into the exact name of the medicinal product.

The action taken towards the medicinal product is also a very important sub-section to fill, it can be: drug withdraw, dose reduced, dose increased, dose not changed, unknown and not applicable. It is also very important to known the result of the re-challenge (68).

In this section the reporter may add a considerable amount of information about the dates and the dosage regime of the medicinal product, which facilitates the pharmaceutical and clinical analysis of the case.
The relation between the suspected(s) drug(s) is reflected in this section, this relation is given by the reporter and by the marketing authorization holder.

**Narrative**

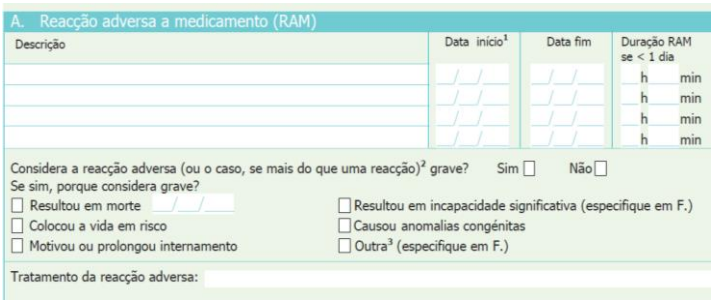
The narrative should contain the following information and, in preference, according to this order:

- The summary of the case with the important data and minimum criteria;
- Description of the beginning and development of the adverse reaction;
- Relation between the suspected medicinal product and the adverse reaction, with the respective dates;
- Treatment and evolution of the adverse reaction;
- Any other relevant information.

In case of a follow up case, the information should be added to the narrative and clearly identified as a follow up with the respective date.

### 6.3.4 Suspected adverse reaction reported by a healthcare professional and consumers

For reports that arise directly from healthcare professionals the analysis of each case is more or less the same as the one described in the previous chapter. Each report may arrive in paper, fax, mail, email, by phone call or directly through the Portal RAM.
The form that can be used by healthcare professionals to report an ADR (71), has the following 6 sections:

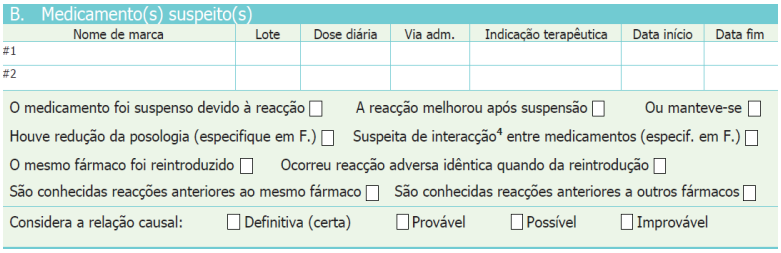

A. Reacção adversa a medicamento (RAM)

| Descrição | Data início[1] | Data fim | Duração RAM se < 1 dia |
|---|---|---|---|
| | / / | / / | h min |
| | / / | / / | h min |
| | / / | / / | h min |
| | / / | / / | h min |

Considera a reacção adversa (ou o caso, se mais do que uma reacção)[2] grave? Sim ☐ Não ☐
Se sim, porque considera grave?
☐ Resultou em morte / / ☐ Resultou em incapacidade significativa (especifique em F.)
☐ Colocou a vida em risco ☐ Causou anomalias congénitas
☐ Motivou ou prolongou internamento ☐ Outra[3] (especifique em F.)

Tratamento da reacção adversa:

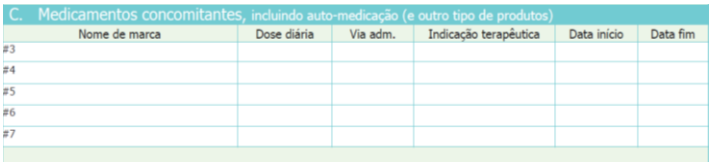
**Figure 12 -** A: Adverse reaction


B. Medicamento(s) suspeito(s)

| Nome de marca | Lote | Dose diária | Via adm. | Indicação terapêutica | Data início | Data fim |
|---|---|---|---|---|---|---|
| #1 | | | | | | |
| #2 | | | | | | |

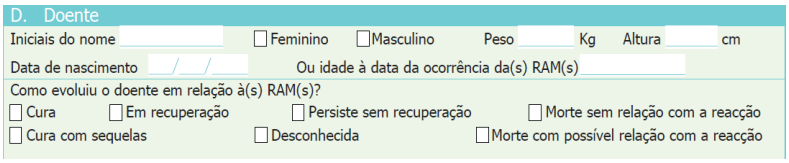
O medicamento foi suspenso devido à reacção ☐ A reacção melhorou após suspensão ☐ Ou manteve-se ☐
Houve redução da posologia (especifique em F.) ☐ Suspeita de interacção[4] entre medicamentos (especif. em F.) ☐
O mesmo fármaco foi reintroduzido ☐ Ocorreu reacção adversa idêntica quando da reintrodução ☐
São conhecidas reacções anteriores ao mesmo fármaco ☐ São conhecidas reacções anteriores a outros fármacos ☐
Considera a relação causal: ☐ Definitiva (certa) ☐ Provável ☐ Possível ☐ Improvável

**Figure 13 -** B: Suspect Medicinal product(s)


C. Medicamentos concomitantes, incluindo auto-medicação (e outro tipo de produtos)

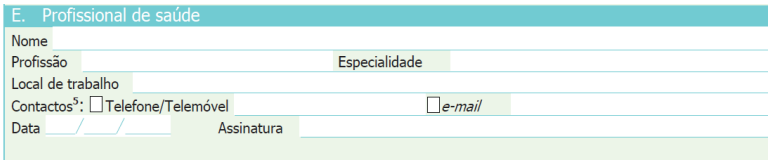
| Nome de marca | Dose diária | Via adm. | Indicação terapêutica | Data início | Data fim |
|---|---|---|---|---|---|
| #3 | | | | | |
| #4 | | | | | |
| #5 | | | | | |
| #6 | | | | | |
| #7 | | | | | |

**Figure 14 -** C: Concomitant medication


D. Doente

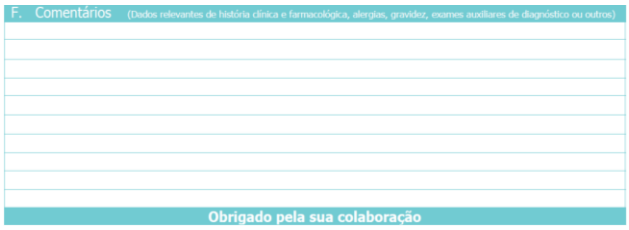
Iniciais do nome ☐ Feminino ☐ Masculino Peso Kg Altura cm
Data de nascimento ___/___/____ Ou idade à data da ocorrência da(s) RAM(s)
Como evoluiu o doente em relação à(s) RAM(s)?
☐ Cura ☐ Em recuperação ☐ Persiste sem recuperação ☐ Morte sem relação com a reacção
☐ Cura com sequelas ☐ Desconhecida ☐ Morte com possível relação com a reacção

**Figure 15 -** D: Patient


E. Profissional de saúde

Nome
Profissão Especialidade
Local de trabalho
Contactos[5]: ☐ Telefone/Telemóvel ☐ *e-mail*
Data ___/___/____ Assinatura

**Figure 16 -** E: Healthcare Professional


F. Comentários (Dados relevantes de história clínica e farmacológica, alergias, gravidez, exames auxiliares de diagnóstico ou outros)

**Obrigado pela sua colaboração**

**Figure 17 -** F: Comments (narrative)

For consumers, the report form (72) is similar, but with simpler language for a better understanding. When a case is written in one of these forms it has to be manually introduced into the SVIG, and the codification has to be done by the technicians at DGRM or Regional Units, because most of the times an adverse reaction or a previous condition of the patients does not come coded in MedDRA but in common language. During the manual insertion of the information, it is normal that certain questions arise. These questions should be appointed and asked to the reporter, in order to better understand the case and improve its quality.

The reports may arrive to DGRM or to one of the 4 regional units. When a case occurred in the continent, then it should be analyzed by the regional unit responsible for the specific area, for example, if it happened in Faro, it should be analyzed by the South regional unit. When a case arrives from one of the Portuguese archipelagos (Azores and Madeira), than it should be analyzed by one of the DGRM technicians, since there is no regional unit there.

As referred previously, the cases may also be directly reported to the web portal (Portal RAM), created due to the new pharmacovigilance legislation that allows the patients/consumers to report any adverse reaction that occurred in Portugal. This is a platform that allows the collection of information on ADRs. The reporting of adverse reactions by health professionals or consumers is essential for the continuous monitoring of the safety of medicines. Upon receipt, the information is evaluated by a team of experts in pharmaceutical and medical safety of drugs, in order to characterize the probability that the reaction described is due to the medication.

#### 6.3.5 Causality assessment

The classification used at DGRM is the WHO scale (73):

**Definitive** – To attribute this category, there has to be a solid clinical evidence or laboratorial modification that occurred with a plausible temporal relation and it cannot be explain by any concomitant diseases or other medicinal products. If the drug is withdrawn and the adverse reaction stopped, and then if the adverse reaction reapers when the medicinal products is reintroduced, the relationship between the suspected medicinal product and the adverse reaction is definitive.

**Probable** – a clinical event or laboratory abnormality with reasonable time relationship to drug intake, the reaction was unlikely caused by other conditions or drugs and the evolution of the adverse reaction after the suspension of the medicinal product is acceptable.

**Possible** - a clinical event or laboratory abnormality that occurs in a relationship that is temporally acceptable, but can also be explained by other conditions or medicinal products and Information on drug withdrawal may be lacking or unclear.

**Unlikely** – a clinical event or laboratory abnormality that occurs in a relationship that temporally unlikely, but not impossible, and the association with other medicinal products or conditions provides a plausible explanation.

**Conditional/Unclassified** – To classify this adverse event is necessary more information to properly evaluate the case.

**Not Classifiable** – This is a report that suggests an adverse reaction, but it not possible to establish causality because the information is contradictory or is insufficient and it cannot be confirmed.

## 6.4 Articulation between the Directorate of Risk Management for Medicines and the Directorate of Inspection and Licensing in quality questions

When a suspicion of quality issue is reported to DGRM it must be also sent to Directorate of Inspection and Licensing (DIL), which is the responsible directorate for the manufacture compliance and quality alerts. In a report with a description of a non-compliance, in which there is no occurrence of ADR, the report is forward to the DIL. However, if an adverse reaction is also described in the mentioned report, it should also be analyzed by DRGM and by DIL. At DGRM, a pharmaceutical and clinical analysis is performed in relation to the adverse reaction.

## 6.5 Intensive Monitoring of Medicines

The intensive monitoring of medicines is performed when there is a special concern about safety or quality of a medicinal product, and it needs to be monitored during a certain period of time. At DGRM this task was performed by the drug safety monitoring group and it consists in the analysis of safety data of a certain medicinal product.

For this purpose, the frequency of analysis is determined by the directorate after a meeting with the technician responsible for this task. Then a series of listings are requested in order to analyze the safety data correspondent to a certain period of time. These listings contain all adverse reactions that occurred with the medicinal product under additional monitoring. The output of the list has to be analyzed to transform the data contained into a report with important conclusions. If any safety issue arises from the listing analysis, this information must be reported and discussed with the Directorate. If the issue is also related with a quality issue of the product, it has to be reported to DIL.

# 7. Article in Pharmacovigilance Bulletin

During my internship I had the chance of being co-author, along with Dr.ª Ana Araújo, of an article with the title: *Nova Legislação de Farmacovigilâcia: Impacto na relação autoridade/notificador*. This article focused on the relationship between INFARMED and the healthcare professionals/consumers in terms of pharmacovigilance. The main discussed topics in the article are:

- The main objective of the new pharmacovigilance legislation and the reason why it was created;
- Describe the main modifications from the previous legislation, such as:
    - Greater involvement of patients in the reporting process, since patients may at their own initiative report ADRs directly to INFARMED.
    - Possibility of consumers, patients and healthcare professionals report an ADR on Portal RAM.
    - Broader definition of ADR, which now includes also, all the ADR that occur outside the terms of MA and the medication errors, overdose, misuse, abuse and off label use.
    - Increase of transparency, with the creation of a national portal linked to the European Medicines Agency website.
    - Public hearings on the safety of medicines, where besides healthcare professionals and the pharmaceutical industry, the general public may also be present.
    - The medicinal products under additional monitoring will be identified, in the SmPCs and PL, by a black colored symbol and an explanatory sentence, relevant and standardized in order to contextualize the need for additional monitoring for that specific medicinal product.
    - Inclusion of a standard text in the SmPC and PL, appealing to the notification of any suspected adverse reaction.

# 8. Conclusion

The INFARMED internship was the most rewarding and fantastic experience of my academic life. Therefore it can be difficult to translate into words in a comprehensive manner all the knowledge and lessons taken from this experience. The opportunity that was given to me, to develop my thesis at DGRM, was very productive and flattering. The work environment was very good, which facilitates the learning process and development my professional and social skills.

I took part of different activities, which contributed to my professional growth. To become more independent and capable of dealing with responsibilities, I had the help and constant support of my colleagues at DGRM.

It also allowed me to analyse the interactions between a Competent Authority, the healthcare professionals and the marketing authorization holders. All my knowledge acquired during the degree in Biomedical Sciences and the Master's Degree in Pharmaceutical Medicine became clearer and easily understood.

The fact that I spent half of my internship in the risk management team and the other half in the medicines' safety monitoring team, allowed me sufficient time to understand how each of these groups work and what type of work is performed by each one.

I also had the chance to follow the entering into force of the new legislation and the development of the new Portal for submission of ICSR by patients and by healthcare professionals, which allowed me to understand the foundations of the new legislation.

This internship allowed me to conclude that the post-authorization stage of a medicinal product is a critical phase in terms of safety data collection and public health protection.

In conclusion, my objectives for the future are the continuous improvement of my skills and acquiring knowledge to be able to carry out my work in pharmacovigilance.

# 9. Appendices

## 9.1 Glossary

**Medicinal Product -** According to the Directive 2001/83/EC a medicinal product is "any substance or combination of substances presented as having properties for treating or preventing disease in human beings or any substance or combination of substances which may be used or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmaceutical, immunological or metabolic action, or to making a medical diagnosis. "

**Individual Case Safety Reports (ICSR) -** An ICSR is the format and content for the reporting of adverse reaction(s) with a medicinal product that occur in a single patient at a specific point of time. It should contain the minimum criteria for reporting, one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at least one suspected medicinal product. (67)

**XML -** eXtensible Markup Language (XML) is the adopted standard for the exchange of Safety and Acknowledgement Messages in the European Economic Area (EEA). (Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)) (74)

**Special situations during reporting of adverse reactions (66):**

***a. Overdose***

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.

***b. Off-label use***

This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.

***c. Misuse***

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.

***d. Abuse***

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

***e. Occupational exposure***

This refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation.

**MedDRA -** MedDRA stands for Medical Dictionary for Regulatory Activities – this a medical terminology that should be used for regulatory documents, to classify adverse event information associated with the use of biopharmaceuticals and other medicinal products. This allows the comprehension of each individual case safety report and reduction of duplicated work. (75)

**EPITT (European Pharmacovigilance Issues Tracking Tool) -** Is a web-based system that effectively tracks and monitors the safety of medicinal products regardless of their authorization type. The objectives include the monitoring of life-cycles of safety signals and safety issues discussed at the level of the Pharmacovigilance Working Party (PhVWP) and hereafter the Pharmacovigilance Risk Assessment Committee (PRAC), the tracking of the Periodic Safety Update Report (PSUR) cycles' and timetables' assessments performed by the National Competent Authorities (NCA) in the context of the PSUR Work Sharing project, and Risk Management activities. (76)

**GVP –** These documents are a set of orientations created to facilitate the performance of pharmacovigilance in the European Union (EU). These guidelines apply to the MAH, to the Agency and to competent authorities, and its aim is to provide a more detailed guidance and improve safety for the patients by strengthening pharmacovigilance across the EU. (44)

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