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Relatório de Estágio Curricular na UFS e no INFARMED, I.P.

Curricular Training Report at the UFS and the INFARMED, I.P.

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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 Professora Doutora Maria Teresa Ferreira Herdeiro, Professora Auxiliar Convidada da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro e da Professora Doutora Maria Augusta Soares, Professora na Faculdade de Farmácia da Universidade de Lisboa e Coordenadora da Unidade de Farmacovigilância do Sul.

Dedico este trabalho aos meus familiares, amigos e a todos aqueles que, de alguma forma, contribuíram para a sua elaboração.

o júri

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palavras-chave

Autoridade Regulamentar, Farmacovigilância, Notificação Espontânea, Reação Adversa a Medicamento, Gestão do Risco, Monitorização de Medicamentos

resumo

O presente relatório descreve a minha experiência de 9 meses enquanto estagiária na Unidade de Farmacovigilância do Sul, uma Unidade Regional de Farmacovigilância do Sistema Nacional de Farmacovigilância e na Direção de Gestão do Risco de Medicamentos da Autoridade Nacional do Medicamento e Produtos de Saúde, I.P..

O principal objectivo deste estágio foi a aquisição de competências técnicas e experiência em farmacovigilância e a consolidação de alguns dos conhecimentos que adquiri durante a Licenciatura em Ciências Biomédicas e o primeiro ano do Mestrado em Biomedicina Farmacêutica.

As atividades desenvolvidas focaram-se, maioritariamente, no processamento de notificações espontâneas de suspeitas de reações adversas provenientes de profissionais de saúde e utentes e na análise da qualidade de notificações de segurança sobre casos individuais enviados pelos titulares de autorização de introdução no mercado. Durante o período de estágio tive ainda a oportunidade de participar em algumas atividades de minimização de risco, tais como a validação de comunicações dirigidas aos profissionais de saúde.

Para além da descrição das actividades e tarefas desempenhadas ao longo do estágio, este relatório pretende também descrever as principais dificuldades sentidas e as competências que considero ter adquirido durante esta experiência profissional.

Este estágio constituiu o meu primeiro contacto com o mundo do trabalho e proporcionou-me uma visão clara de como funciona uma Unidade Regional de Farmacovigilância e uma Autoridade Nacional do Medicamento, bem como as suas interações com a indústria farmacêutica, os profissionais de saúde e os utentes, possibilitando-me, simultaneamente, a aquisição de variadas competências a nível pessoal e profissional, essenciais para o meu futuro.

keywords

Regulatory Authority, Pharmacovigilance, Spontaneous Report, Adverse Drug Reaction, Risk Management, Drug Monitoring

abstract

The present report describes my 9 months experience as a trainee at the Southern Pharmacovigilance Unit, a Regional Pharmacovigilance Unit of the National Pharmacovigilance System and at the Risk Management for Medicines Department of the National Authority of Medicines and Health Products, I.P..

The main objective of this training was the acquisition of technical skills and experience in pharmacovigilance and the consolidation of some knowledge acquired during my Degree in Biomedical Sciences and my first year of the Master's Degree in Pharmaceutical Biomedicine.

The activities developed focused mostly on the processing of spontaneous reports of suspected adverse drug reactions from healthcare professionals and patients and on the analysis of the quality of individual case safety reports sent from the marketing authorisation holders. During the training period I also had the opportunity to participate in some risk minimisation activities, such as the validation of direct healthcare professional communications.

Besides the description of the activities and tasks performed over the period of the training, this report also describes the main difficulties encountered and the competencies that I believe I achieved during this professional experience.

This training was my first contact with the work environment and gave me a clear perspective of how a Regional Pharmacovigilance Unit and a National Competent Authority work, as well as their interactions with the pharmaceutical industry, the healthcare professionals and the patients, allowing me, simultaneously, to acquire several competences at a personal and professional level, which will be essential for my future.

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List of Abbreviations:

ACK – Acknowledgement

ADR – Adverse Drug Reaction

CA – Competent Authority

CHMP – Committee for Medicinal Products for Human Use

CIOMS – Council for International Organizations for Medical Sciences

CMD(h) – Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

DGRM – *Direção de Gestão do Risco do Medicamento* (Risk Management for Medicines Department)

DHPC – Direct Healthcare Professional Communication

DIL – *Direção de Inspeção e Licenciamento* (Inspections and Licensing Department)

EC – European Commission

EMA – European Medicines Agency

EU – European Union

EV – EudraVigilance

FFUL – *Faculdade de Farmácia da Universidade de Lisboa* (Faculty of Pharmacy of the University of Lisbon)

GVP – Good Pharmacovigilance Practices

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

ICSR – Individual Case Safety Report

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

MA – Marketing Authorisation

MAH – Marketing Authorisation Holder

MedDRA – Medical Dictionary for Regulatory Activities

MS – Member State

NPS – National Pharmacovigilance System

NUI – Non-Urgent Information

PAES – Post-Authorisation Efficacy Studies

PASS – Post-Authorisation Safety Studies

PIL – Patient Information Leaflet

PRAC – Pharmacovigilance Risk Assessment Committee

PSUR – Periodic Safety Update Report

RA – Rapid Alert

RMP – Risk Management Plan

RPU – *Unidade Regional de Farmacovigilância* (Regional Pharmacovigilance Unit)

SmPC – Summary of Product Characteristics

SOC – System Organ Class

SR – Spontaneous Report

SVIG - *Sistema de Vigilância* (Vigilance System)

UFS – *Unidade Farmacovigilância do Sul* (Southern Regional Pharmacovigilance Unit)

UMC – Uppsala Monitoring Centre

WHO – World Health Organization

XML – Extensible Mark-up Language

1 Introduction

The present report describes my curricular training, a part of the Master's degree in Pharmaceutical Biomedicine. This training experience took place in two institutions: *Unidade de Farmacovigilância do Sul* (Southern Regional Pharmacovigilance Unit) (UFS), from October 1st 2012 to March 29th 2013, and in the *Direção de Gestão do Risco de Medicamentos* (Risk Management for Medicines Department) (DGRM) of the *Autoridade Nacional do Medicamento e Produtos de Saúde*, I.P. (National Authority of Medicines and Health Products, I.P.) (INFARMED, I.P.), from May 2nd 2013 to July 26th 2013.

Regarding the content of this report, the state of the art is presented, including a historical perspective of Pharmacovigilance, the National Pharmacovigilance System and the new European Pharmacovigilance Legislation. Then, it is provided an overview of the host institutions and the objectives I defined for my training. Next, it is made a description of the specific activities I had the opportunity to perform during my curricular training and the complementary learning. After this, it is made a discussion about my experience, the main encountered difficulties and the learning outcomes achieved. Finally, a conclusion about the whole experience is presented.

The main objective of this 9-month training in the area of pharmacovigilance was to consolidate and complement the knowledge acquired in my degree and master and apply it in a real work environment.

1.1 State of the Art

This section intends to provide a brief overview of the current state of the art in the area of pharmacovigilance within the European Union (EU), since the activities developed during my curricular training were related to this area.

Medicinal products have considerably contributed for numerous benefits to the health of the patients, preventing millions of deaths (1). In fact, medicinal products have changed the way in which diseases are controlled, largely contributing to the improvement of quality and average life expectancy (2, 3). However, for all medicinal products there is a trade-off between the benefits and the potential for harm and, as stated in a report by the United Kingdom Committee on Safety of Drugs in 1969/1970,

“No drug which is pharmacologically effective is entirely without hazard. The hazard may be insignificant or may be acceptable in relation to the therapeutic action of the medicinal product. Furthermore, not all hazards can be known before a drug is marketed” (4). This phrase summarises the relativity of the concept of safety and the need for constant surveillance of the safety profile of marketed medicinal products.

1.1.1 Pharmacovigilance – Historical Perspective

Pharmacovigilance is defined by the World Health Organization (WHO) as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem” (5). Therefore, this science assumes a crucial role on the evaluation of the risks and benefits of drugs, being a fundamental tool to guarantee the safety of medicinal products and, consequently, the protection of public health. Although the pharmacovigilance is present in the early stages of the development of medicines, it is during the post-authorisation phase that it plays a key role, since it is in this phase that the benefit-risk balance of the medicinal products is in constant re-analysis.

During the pre-marketing phase, all medicines have already been subjected to several studies in order to determine their safety and efficacy profiles. However, the data collected before the drug is marketed is far from being sufficient to create a complete safety profile of the drug, since it is difficult to detect most of the adverse drug reactions (ADRs) based on these data, especially those rare and the ones that manifest after a prolonged use (6, 7). In fact, clinical trials are conducted in a controlled environment, in a homogeneous and relatively small sample of individuals, with restricted inclusion and exclusion criteria, for a limited period. Obviously, this selected population from clinical trials is very different from the one who will use the drug in the real context of clinical practice (8-10). Thus, many serious ADRs are only detected after a medicinal product has been in the market for several years, being used by a wide, heterogeneous population (6-8). These facts highlight the need for continuing to monitor the safety and efficacy of the medicinal products throughout its lifecycle (7, 9).

The concepts of “safety” and “doing no harm” have already been mentioned in the Hammurabi Code (2,200 b.C.) – “The Doctor who causes death should lose his hands” –, Homer's Odyssey (950 b.C.) – “Many drugs are excellent when isolated or mixed, but

many of them are fatal" – and, later, by Hippocrates (460-370 b.C.) – "P*rimum non nocere*" (11). However, only after the thalidomide disaster did the world become conscious of the danger of unforeseen accidents caused by medicinal products considered safe (11, 12). Thalidomide was an unsafe medicine used in Europe, Australia and Japan from 1956 to 1961 by pregnant mothers to treat nausea, resulting in thousands of infants that were born with phocomelia and micromelia, as a consequence of their exposure to the medicine during gestation (13). Most of these phocomelia cases could have been avoided if there were organised safety monitoring systems at that time that would lead to a much earlier detection of the thalidomide teratogenicity. Therefore, this tragedy marked not only a turning point in the Marketing Authorisation (MA) regulation and toxicity testing of medicines, but also brought the importance of drug safety monitoring systems to attention, which gave rise to the first international efforts to address drug safety problems (12, 14). In fact, in response to this tragedy, in 1963, the Sixteenth World Health Assembly reiterated the need for early action in order to allow a faster dissemination of information on ADRs and led to the initiation of the WHO Programme for International Drug Monitoring, in 1968, with the aim of creating an international system to detect unknown or poorly understood ADRs to date. From that date on, several systems to collect adverse drug reactions were created in WHO Member States to enable a constant monitoring of the benefits and risks of medicinal products. The Uppsala Monitoring Centre (UMC), which coordinates the WHO Programme since 1978, collects, processes and stores the cases of ADRs received from the member states (MSs).

The WHO programme created in the 60's led to the emergence of the science of pharmacovigilance and to the creation of different national pharmacovigilance systems that still exist today worldwide (11, 12, 15). In the last years, the number of member countries participating in the WHO programme has increased (currently there are 117 official member countries, including Portugal) and pharmacovigilance is having an increasingly more relevant role in clinical practice and in the improvement of the public health (12, 16).

The consequences of all these efforts are that in the last decades several medicinal products have been withdrawn because of the discovery of potential threats during their use, as is the case of cerivastatine (Lipobay®), which was voluntarily withdrawn from the world market in 2001, after reports of fatal rhabdomyolysis generating a safety alert signal (17), and, more recently, the case of rofecoxib (Vioxx®), one of the most widely

used medicines that was withdrawn from the market, in 2004, due to findings of cardiovascular adverse effects in patients using this medicine (18).

However, in spite of the progress made so far in the field of pharmacovigilance, the burden of ADRs is still substantial. In fact, ADRs remain an evident public health problem on a global scale, being an important cause of mortality and morbidity in developed countries, not to mention the high financial costs associated to them. According to a meta-analysis conducted by Lazarou, et al. (1998), in the United States of America, over 2 million people suffer serious ADRs every year, from which 106,000 are fatal, putting ADRs between the fourth and sixth place among all the causes of death in the United States of America, after cardiac diseases, cancer and strokes, which has a direct annual cost of about 1.56 to 4.0 billion dollars (19). On an European level, it is worth mentioning the study conducted by Pirmohamed, et al. (2004) in the United Kingdom, which demonstrated that 1 in 16 hospital admissions is caused by ADRs (20). In 2008, the European Commission (EC) published the proposals for strengthening the pharmacovigilance to reduce adverse effects of medicines, concluding that ADRs are the fifth most common cause of hospital death and are responsible for 197,000 deaths per year in the EU, with a total cost for society of €79 billion (1).

It is possible to minimise the risks from the use of medicinal products by ensuring its rational use through pharmacovigilance measures. Therefore, the utter need for a post-marketing surveillance through pharmacovigilance activities, namely the reporting and analysis of the ADRs, as well as the effective communication to the healthcare professionals and the patients, is easily understood.

1.1.2 National Pharmacovigilance System

The National Pharmacovigilance System (NPS) is currently constituted by the DGRM of the INFARMED, I.P., responsible for its coordination, four Regional Pharmacovigilance Units (RPUs), the marketing authorisation holders (MAHs), the healthcare professionals, the Health Services and, more recently, the consumers (21). Its primary objectives are the evaluation of the safety profile of marketed drugs and the implementation of actions that allow to minimise the risks derived from the use of the medicinal products (15).

The first official rule in Portugal that mentioned the Pharmacovigilance was the Decree-Law No 72/91 of 8 February 1991 (posteriorly revoked by the Decree-Law No176/2006 of 30 August 2006), which states that the MAHs, physicians, technical directors of pharmacies and other health technicians should communicate to the *Direção Geral de Assuntos Farmacêuticos* the adverse reactions resulting from the use of medicinal products that they have had knowledge, creating a National Pharmacovigilance System (22). In 1992, the regulatory dispatch 107/92 of 27 June 1992, announces the creation of the Portuguese Pharmacovigilance System. In the beginning, it worked in the Medicine Study Centre, being integrated into the INFARMED, I.P. in 1993, when it was created (23). Having been established in a centralised way, it did not take a long time to understand the importance of decentralising it geographically (15). As such, in 1999, the Ordinance No 605/99 of 5 August 1999 predicted the creation of RPUs in Portugal, on an attempt to improve the performance of the system (11, 23, 24). It was under this law and after public tender that four Regional Units of Pharmacovigilance were created, in the mid-2000: Northern Regional Pharmacovigilance Unit, Centre Regional Pharmacovigilance Unit, Southern Regional Pharmacovigilance Unit (UFS) and Azorean Pharmacovigilance Regional Unit (currently deactivated) (11). In 2003 there was a restructuring of the RPUs, with the redefinition of the geographical area correspondent to the UFS, which changed its name to Lisbon and Tagus Valley Regional Pharmacovigilance Unit and with the creation of a new regional unit - the Southern Regional Pharmacovigilance Unit -, which area of activity is the southern Regional Health Administration (15). This way, the NPS became truly decentralised, ensuring a larger proximity to the reporters, involving academic and hospital establishments, improving the technical-scientific capacity in pharmacovigilance, divulging the system and fomenting the reporting of ADRs (15). In fact, the start of the RPUs coincided with the significant increase in the number of reports of suspected ADRs (23), as presented in Figure 1 (25).

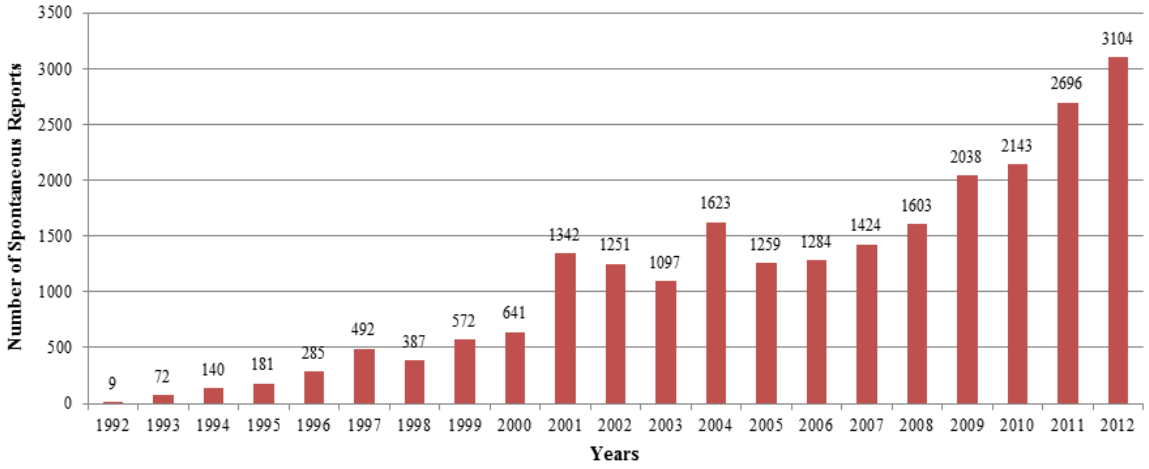

Figure 1 – Number of ADR reports received in the NPS[1]

In 2002, the Ordinance No 605/99 was revoked and the Decree-Law No 242/2002 of 5 November 2002 was created to apply the European Community Directive 2001/83/EC of 6 November 2001 to the Portuguese legislation, in terms of Pharmacovigilance, establishing the scope, objectives and organisation of the NPS, the roles of the INFARMED, I.P., RPUs, healthcare professionals and MAHs in this system (26).

In 2006, the Decree-Law No 242/2002 was revoked by the Decree-Law No 176/2006 of 30 August (*Estatuto do Medicamento*), which grouped all pharmaceutical legislation related to the medicinal products for human use, transposing the community legislation to the national legislation. This Decree-Law sets a strong change in the medicines sector, namely the areas of manufacturing, quality control, safety and efficacy, market introduction and commercialisation of the medicinal products for human use. Concerning pharmacovigilance matters, this regulatory paper mentions that all the suspected serious and unexpected ADRs should be reported to the INFARMED, I.P. or RPUs, by the healthcare professionals. The MAHs responsibilities in the scope of pharmacovigilance are also described in this Decree-Law (27).

Recently, the Decree-Law No 176/2006 was amended by the eighth time with the approval of the Decree-Law No 128/2013 of 5 September 2013, which transposes into national legislation the Directive 2011/62/EU of 8 June 2011 and the Directive 2012/26/EU of 25 October 2012, changing the Decree-Law No 20/2013 of 20 February

[1] Evolution of the number of ADR reports between 1992 and 2012 in Portugal.

2013, which in turn transposed the Directive 2010/84/EC into the Portuguese law (21, 28).

Currently, there are four RPUs that cover all the continental territory: Northern Regional Pharmacovigilance Unit, Centre Regional Pharmacovigilance Unit, Lisbon and Tagus Valley Regional Pharmacovigilance Unit and Southern Regional Pharmacovigilance Unit, which receive and process the spontaneous reports (SRs) from the concerning geographical areas, respectively to the Regional Health Administration of North, Centre, Lisbon and Tagus Valley, Alentejo and Algarve (29). Considering there are currently no Pharmacovigilance Units in the Azores and Madeira, the SRs from these regions are processed by the INFARMED, I.P. (Figure 2).

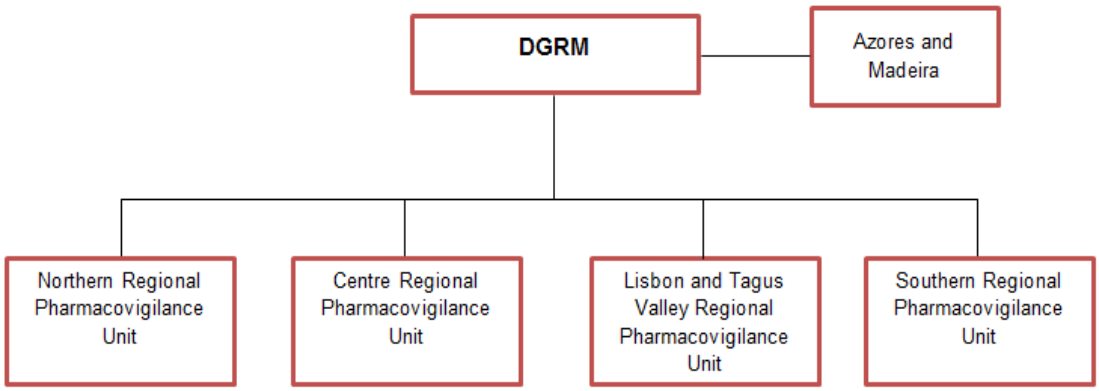

Figure 2 – Part of the NPS: relation between the DGRM and the RPUs[2]

INFARMED, I.P. is also responsible for sending the information of all cases of ADRs occurred in Portugal for the European and worldwide ADR databases, EudraVigilance (EV) and VigiBase, respectively (29). The EV is a central database created by the European Medicines Agency (EMA) in 2001 that contains adverse reaction reports to the medicinal products licensed in the EU, which were received from the regulatory agencies and from pharmaceutical companies (30). The VigiBase is a global database of Individual Case Safety Report (ICSRs), created in 1968 by the WHO, being currently monitored and maintained by the UMC, situated in Uppsala, Sweden. It

[2] The four RPUs submit the ADR reports received from each geographical area to the DGRM. The ADR reports from Azores and Madeira are processed directly by the DGRM.

consists of reports of adverse reactions received from the countries that are members of this programme (31).

Figure 3 presents, summarily, the several partners that directly and indirectly integrate the structure of the NPS, as well as the circuit of the information on suspected ADRs between the various partners.

Figure 3 – Structure and functioning of the NPS and its network on safety information at an European and worldwide level [3]

Therefore, the NPS, along with the pharmacovigilance systems of the other MSs of the EU, constitutes a crucial element of the wide net of exchange of information at an European and worldwide level, essential to improve the knowledge of the safety profile of marketed drugs (23).

When looking to the Figure 1, it is noticeable that the number of SRs in 2011 was the quadruple of the verified in 2000, making evident the evolution that the NPS has gone through in the last years. On a time where the NPS celebrates its second decade of existence, during which there were more than 20,000 SRs received (29) and

[3] Subtitles: the dashed arrow means that the direct sending of non-serious ADRs and serious ADRs occurred within the EU from MAHs to the EMA will only be possible when EV database is completely operational. Until then, the serious ADRs occurred within the EU will be sent to the CA of the MS where the case occurred and, similarly, the non-serious ADRs occurred within the EU are sent to the CA of the MS where the case occurred, if solicited (the DGRM will not solicit this information, by routine). The serious ADRs occurred outside the EU, however, are already sent by the MAHs directly to the EV.

successfully achieved the commitments of Portugal together with the EC in the pharmacovigilance area (the number of SRs received by the NPS has already surpassed the number recommended by the WHO of 200 reports/million inhabitants), this system is now mature and it seems that it is prepared to a new adaptation with the implementation of the recent European Pharmacovigilance legislation and deal with the several challenges that arise from it (29).

1.1.3. New European Pharmacovigilance Legislation

The science of Pharmacovigilance went through several modifications over the last few years with the new European Pharmacovigilance Legislation. This legislation was initially published in December 2010 and, despite having entered into effect in July 2012, it has not yet been fully implemented. It was created to improve patients' safety and public health and brings substantial changes to the Pharmacovigilance systems in the EU. In fact, it constitutes the biggest change to the regulation of medicines of human use in the EU since 1995 (32). The new legislation comprises the Directive 2010/84/EU of 15 December 2010 amending Directive 2001/83/EC and the Regulation No 1235/2010 of 15 December 2010 amending Regulation No 726/2004 and Regulation No 1394/2007 (33, 34). While the Regulation became immediately applicable in all MSs (since it does not require any transposition by the national authorities), the Directive was transposed into the Portuguese legislation with the Decree-Law 20/2013 of 14 February 2013 (35), meanwhile altered by the Decree-Law 128/2013 of 5 September 2013 (21). In 2012, another Directive and Regulation were published: Directive 2012/26/EU of 25 October 2012 amending Directive 2001/83/EC, which was transposed into the Portuguese legislation with the Decree-Law 128/2013 and the Regulation No 1027/2012 of 25 October 2012 amending Regulation (EC) No 726/2004 (36, 37). This legislation is accompanied by the Commission Implementing Regulation No 520/2012 of 19 June 2012, which provides details on the operational aspects of the new pharmacovigilance legislation (38).

To support this new legislation, a new set of guidelines were developed – the Good Pharmacovigilance Practices (GVP). Specifically, the GVP are a set of measures developed to facilitate the performance of pharmacovigilance in the EU. This guideline replaces the Volume 9A of the Rules Governing Medicinal Products and applies to the

EMA, the MAHs and Competent Authorities of the MSs. The GVP guideline includes chapters on product- or population-specific considerations and modules (from I to XVI), each one covering a major pharmacovigilance process. Most modules are available in their final versions and the full set of modules is expected to be available during 2013 (39). The Volume 9A remains the reference document for the topics covered in GVP modules that are not published as final (40).

The new legislation was created with the following objectives (41):

- To increase the planning, efficiency and proactivity (focusing on prevention) of the European pharmacovigilance system;
- To promote pharmacovigilance based on the evidenced risk and proportional to it;
- To enhance the quality of safety data;
- To ensure fast and robust (evidence based) decision-making procedures in the EU;
- To simplify procedures and reduce the duplication of effort, in a work-sharing perspective (allowing a more efficient use of the resources in the EU);
- To make roles and responsibilities more clear for all parties (EMA, CAs, MAHs);
- To promote the involvement of patients and healthcare professionals in the pharmacovigilance;
- To increase the transparency of the pharmacovigilance activities;
- To improve the information on medicinal products.

One of the major pillars of this legislation is the increased transparency and communication, through the publication of pharmacovigilance information of the medicinal products authorised in the EU, public hearings as well as coordination of safety messages between MSs (41). As such, it was created a new pharmacovigilance committee in the EMA - the Pharmacovigilance Risk Assessment Committee (PRAC) -, which strengths the role of the EMA in improving the coordination between MSs (35). The PRAC is the responsible committee for the evaluation of safety information and makes recommendations to the Committee for Medicinal Products for Human Use (CHMP) and Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human (CMD(h)) on questions related to pharmacovigilance activities of medicines for human use in the EU. This committee assesses all aspects of risk

management of medicines for human use, including the detection and evaluation of the ADRs and subsequent risk communication (42). It is also responsible for the evaluation of periodic update safety reports (PSURs) and risk management plans (RMPs), pharmacovigilance audits, for the design and evaluation of post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES), the management and prioritisation of safety signals and to make recommendations to the additional monitoring list (41).

Among the many changes brought by this legislation, there was the enlargement of the ADR definition, in order to cover any noxious and unintended effects resulting not only from the authorised use of a medicinal product, but also from use outside the terms of the marketing authorisation, including the use off-label, abuse, misuse, overdose, medication errors and occupational exposure (33). With the new legislation there is also the inclusion of the consumers in the pharmacovigilance systems in all EU, as reporters of suspected ADRs and also being engaged in decision-making processes, as a way of empowering the consumers.

Another objective of the new pharmacovigilance legislation is to strengthen the role of the EV as the EU central database. It is intended that this database becomes the single point of receipt for pharmacovigilance information concerning all the medicinal products for human use authorised in the EU. Therefore, both the CAs and the MAHs will submit all the reports of ADRs electronically, directly to the EV (33). However, the direct sending of ADRs from MAHs to EV will only be possible when this database is completely operational (33), which is estimated to be in 2015 (43).

Other requirement of the new legislation is the publication of a European additional monitoring list. The medicinal products included in this list are subjected to a closer monitoring by the regulatory authorities. This list comes from the need of analysing the uncertainties regarding the benefit-risk balance of a certain medicinal product. The products included in this list will be identified by a black inverted triangle and a standardised sentence in the SmPC and PIL declaring that the medicinal product is subject to additional monitoring, encouraging the reporting of ADR (44, 45). The aim of this is to foster the transparency and communication with healthcare professionals and consumers. A medicine can be included in this list in every phase of its life cycle and remains under additional monitoring for five years or until PRAC decides to remove it from the list (45). All the new active substances authorised in the EU after 1 January 2011 gets the additional monitoring status (44, 45).

This legislation also brought changes in the content and submission of PSURs and RMPs, in order to integrate the concepts of benefit-risk balance and risk minimisation measures, allowing a proactive and proportionate risk management.

The PSURs have now a different structure with 22 chapters and their scope changed to a benefit-risk analysis based on cumulative data rather than only a presentation of safety data related to a specific period. The presentation of line listings with the ADRs will no longer be necessary, since this information will be in the EV. The obligations to PSUR submission are now proportionate to the risks posed by the medicinal products, so generics, homeopathic, traditional herbal and well-established use medicinal products are exempted from submitting PSURs, except in specific circumstances (for example when it is specifically requested by the regulatory authorities) (46). In a work-sharing perspective, there will be a single assessment of PSURs with the same active substance or combination of active substances. Therefore, the dates and frequency for submission of PSURs must be harmonised. These dates are specified in the EMA's European Union Reference Date list. In line with the concept of transparency, the results of the PSURs assessment are, later, made public by the EMA (40, 46).

The RMP, which describes, in detail, the risk management system used by the MAH, became mandatory for all the new MAs. The risk management system should be proportionate to the identified and potential risks, as well as to the need of post-authorisation safety data. The RMP can be submitted at any time during the product's life cycle, by the MAH's initiative or by CA's request. It has also a different structure with 7 parts sub-divided in modules, rather than the 2 parts that it had until now. This modular structure allows a higher flexibility to make changes to the plan. With this new legislation, the summaries of the RMPs will be available for the public with information specifically for the consumers. Also, besides the implementation of risk minimisation activities, it is now required to monitor their effectiveness (40, 47).

There were also changes in the authorisation requirements, such as the obligation to submit PASS and PAES. In fact, non-interventional PASS and PAES can be now imposed as a condition to grant a MA. There is also a new definition, format and content of the protocols, abstracts and study final reports for the PASS. Therefore, the PASS is, according to the Directive 2010/84/EC, any study with an authorised medicinal product with the aim to identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product or of measuring the

effectiveness of risk management measures (33). These studies can be initiated, managed or financed voluntarily by the MAH or through obligation imposed by the CA. The PASS will be registered on a European database, the EU PAS Register, in order to increase the transparency and avoid unnecessary duplication of efforts (40, 48).

As already stated, this legislation brings huge changes to the pharmacovigilance processes, and its implementation involves, evidently, high human and financial resources. Therefore, it is being implemented in stages and some of the changes will only be applicable in the upcoming years.

1.2 Vision about the Institutions – Southern Regional Pharmacovigilance Unit & INFARMED, I.P.

1.2.1 Southern Regional Pharmacovigilance Unit

The Southern Regional Pharmacovigilance Unit (UFS) is one of the RPUs of the Portuguese Pharmacovigilance System, which activity is in the districts of Faro, Beja, Évora, Portalegre and some municipalities of Setúbal and is funded by the National Authority of Medicines and Health Products (INFARMED, I.P.) (49). It was created in 2004, with the establishment of a protocol between the Faculty of Pharmacy of the University of Lisbon (FFUL) and the INFARMED I.P.. This unit is coordinated by the INFARMED's Pharmacovigilance Department - the DGRM -, and collaborates with them on the execution of its duties, despite having technical and administrative autonomy. The location of the UFS in an institution of higher education allows a better access to technical and scientific tools, enabling the realisation of pharmacovigilance and pharmacoepidemiology studies that are a part of thesis of Masters/Doctorates, as well as an easier integration of students as trainees in the UFS.

The UFS is coordinated by the Prof.ª Doutora Maria Augusta Soares, and its activities are managed by a pharmacovigilance technician, which is responsible for the training and processing of spontaneous reporting of ADR. Besides, UFS currently has a part time trainee, which aids in the daily activities of the unit. The person responsible for the attribution of causality to the reports of ADR received is a physician in the *Hospital de Santa Maria* in Lisbon. Besides this team, the UFS counts on the

collaboration of several healthcare professionals. In fact, as a way to reinforce the cooperation with the healthcare professionals, the UFS established a project of creation of dynamising elements of pharmacovigilance with the cooperation of healthcare institutions of the southern region, establishing, in a pioneer way, the role of pharmacovigilance representatives. These figures are healthcare professionals that develop activities in the pharmacovigilance area, in articulation with the RPUs or with the DGRM of the INFARMED, I.P. and have, in the healthcare institutions where they exercise their functions, the role of divulging, to the other healthcare professionals, the NPS and promoting the sending of SRs of suspected ADRs to the RPUs or to the DGRM. Currently, the UFS has eight pharmacovigilance representatives, all of them pharmacists by profession in several health institutions of the south of Portugal. These pharmacovigilance representatives have been responsible for a considerable increase in the SRs received by the UFS.

Concerning the activities performed by the UFS, these can basically be divided in 4 areas that are included in 2 levels, according to their importance and priority. Thus, the activities conducted by the UFS considered a priority are included in level 1, which consist of processing SRs and divulgation of pharmacovigilance, while level 2 includes investigation and training. More specifically, and according to the Decree-Law 176/2006, it is the responsibility of the pharmacovigilance units to carry out the following activities: reception, classification, processing and validation of the SRs of suspected ADRs, including the process of determining the causal relationship, while guarantying the utmost confidentiality of the data; divulgation and promotion of the SRs of ADRs in their geographical area; presentation of proposals for the realisation of pharmacoepidemiology studies within the NPS; elaboration and periodic presentation of the result of the activities performed to the INFARMED, I.P.; collaboration with the DGRM on the preparation of relevant information to be distributed to other regional units or to the international authorities, and on the organisation of training sessions about pharmacovigilance; notifying the DGRM of the reports of suspected ADRs that the unit receives or has knowledge of.

1.2.2 INFARMED, I.P.

The *Instituto Nacional da Farmácia e do Medicamento* (National Institute of Pharmacy and Medicines) (INFARMED, I.P.), now called *Autoridade Nacional do Medicamento e Produtos de Saúde I.P.* (National Authority of Medicines and Health Products, I.P.) was founded in 1993, through the Decree-Law No 353/93 of October 7, grouping all the roles related to the medicines that were thus far disperse or non-existent, including the integration of the NPS, which until then was integrated at the Medicine Study Centre.

INFARMED, I.P. is the national Regulatory Authority under the aegis of the Health Ministry responsible for the evaluation, authorisation, discipline, inspection and production control, distribution, commercialisation and use of human medicines and health products (including cosmetic and body hygiene products and medical devices) in Portugal, with the ultimate purpose of protecting the Public Health (50). Therefore, it is a public institution indirectly administered by the State, with administrative and financial autonomy (51). It is located in Lisbon and has jurisdiction over the entire national territory.

The main activities performed by the INFARMED, I.P. regarding the medicines for human use are illustrated in Figure 4 (52).

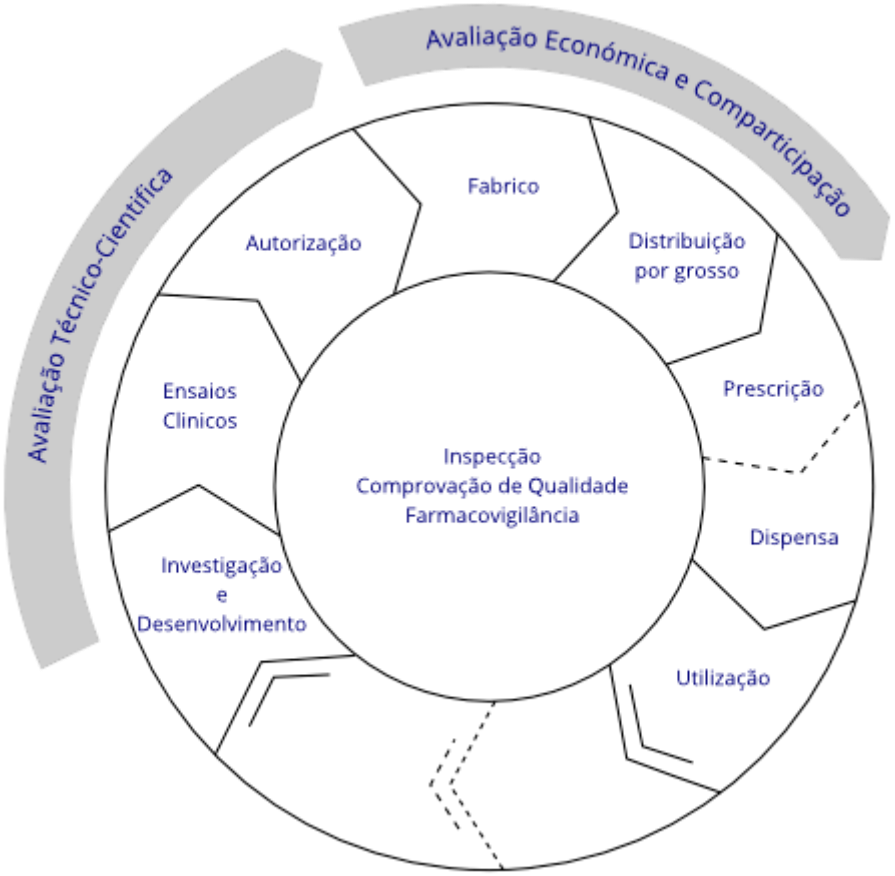

Figure 4 – Interactive life-cycle of a medicine for human use[4]

Relatively to its structure and organisation, INFARMED, I.P. is composed by a management body, eight business functions and three supporting functions. The business functions are: Medicines Evaluation Department, Risk Management for Medicines Department, Heath Products Department, Inspections and Licensing Department, Quality Verification Department, Economic and Marketing Evaluation Department, Information and Communication Management Department and Notified Body. The organisational chart of INFARMED I.P. is presented in Figure 5 (53).

[4] The several intervenients (manufacturers, distributors, prescribers, pharmacies, other points of sale and consumers) are subject to several obligations and procedures and the INFARMED, I.P. is responsible for accompanying and assuring their compliance. In this figure, it is possible to see that the pharmacovigilance is transversal to all the life cycle of a product, being present in all the activities of this cycle, since the product's investigation to its use by the patients.

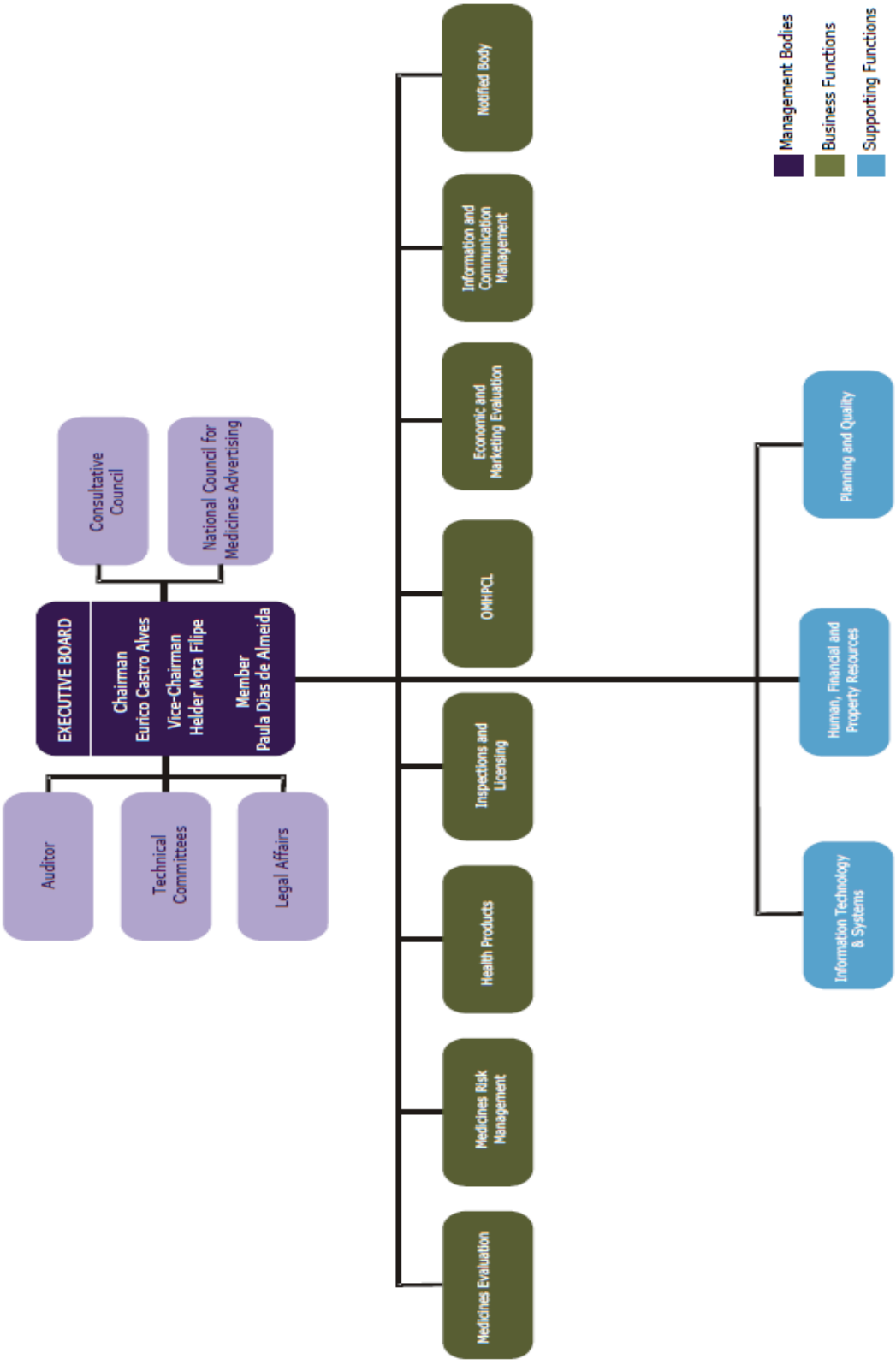

Figure 5 – INFARMED's organisational chart

1.2.2.1 Risk Management for Medicines Department

My internship at INFARMED, I.P. took place in the Risk Management for Medicines Department (DGRM). The DGRM is the organic unity of INFARMED, I.P. that coordinates the NPS of human medicines, namely in respect to the collection, evaluation and dissemination of information on suspected adverse drug reactions, the analysis of causal relationships between medicinal products and adverse reactions and the early identification of safety problems with the use of medicinal products. Besides that, it has the following responsibilities (54, 55):

- To manage the EU pharmacovigilance alerts system and ensure the participation in the WHO Programme for International Drug Monitoring;
- To ensure the safety monitoring of medicines through the RMPs and PSURs;
- To promote and perform epidemiological studies, propose and implement safety measures and benefit-risk reports;
- To collaborate with national/international entities in the execution of studies in the field of medicines' epidemiology;
- To coordinate the activities of pharmacovigilance units that integrate the NPS;
- To ensure the dissemination of safety information to the health professionals and general public;
- To ensure the elaboration of standards and orientations for the users Infarmed's services;
- To ensure the articulation with the evaluation of medicines commission on pharmacovigilance issues;
- To collaborate in the activities of regulatory and scientific advice;
- To ensure the national and international representation of the INFARMED, I.P. within its attributions.

Inside DGRM, there are four teams. Each team is responsible for different activities and has 3 to 5 people, with different backgrounds (although most of them are pharmacists). Basically, two of the teams are responsible for the collection and evaluation of ADRs reports and the sending of ADR information to internal and external partners. However, while one of the teams is responsible for managing the reports that come from the MAHs, the other one is responsible for processing the reports of healthcare professionals and consumers from Madeira and Azores as well as

managing the reports already processed by the pharmacovigilance units. Other team is responsible for the activities of risk minimisation and another one performs searches and manages safety signals. The latter team also coordinates the electronic transmission of ICSRs. All these teams are coordinated by the Director of the DGRM, Dra. Alexandra Pêgo.

The activities I developed during my curricular training in DGRM were mainly related with the management of the reports from the MAHs. However, I had also the opportunity to get involved in some of the risk minimisation activities.

1.3 Training Objectives

The general objective of this 9-month training in the area of pharmacovigilance is to consolidate and complement the multi-disciplinary knowledge acquired in my academic formation through the involvement in the daily work of a pharmacovigilance unit and a pharmacovigilance department at a regulatory authority. Additionally, I have defined a more specific set of objectives for this training:

- To develop a deep understanding about the pharmacovigilance procedures and regulatory framework;
- To know the structure and activities performed by a pharmacovigilance unit and a regulatory authority for medicines and how these articulate with the EMA;
- To understand the articulation of the national pharmacovigilance system and its connection with the EMA and WHO;
- To be able to autonomously and efficiently perform the procedures involved with the processing of SRs and ICSRs;
- To obtain experience in medicinal products' monitoring and risk management;
- To enhance my intrapersonal skills, such as autonomy, self-confidence, responsibility sense, problem solving, critical thinking and time management;
- To increase social and interpersonal skills related to teamwork and communication;
- To establish a working contact network.

2 On-the-job Training

2.1 Activities Developed at the Southern Regional Pharmacovigilance Unit

This section of the report intends to describe all the activities and tasks developed during my curricular training at the UFS.

2.1.1 Spontaneous Reports of Suspected Adverse Drug Reactions

The Portuguese Pharmacovigilance System is essentially based on the system of spontaneous reporting, similarly to what is seen in the other European countries (56, 57). This method consists on the voluntary reporting of noxious and unintended responses that come from the use of a medicinal product - also known as suspected medicinal product - by healthcare professionals and, with the entry into force of the new pharmacovigilance legislation, by the consumers themselves, to the DGRM, the RPUs or to the MAHs. The SRs sent to the RPUs and to the MAHs have to be later analysed by the INFARMED, I.P..

The report of ADRs was done, until July 2012, by the filling of an ADR Reporting Form, on paper format, by healthcare professionals only (Appendix A1), by e-mail, by telephone or, in the cases of Northern and Southern RPUs, by an online form available in the website of these RPUs.

With the new pharmacovigilance legislation, a web portal, named PortalRAM, was introduced in August 2012, where it is possible for any individual (healthcare professional or not) to report suspicions of ADRs. PortalRAM is available through the INFARMED's and RPUs websites. This portal was created as a mean of facilitating and speeding up the procedure of spontaneous reporting in Portugal, improving and increasing the participation of the healthcare professionals in the NPS and empowering the consumers. The reporting by paper format is still accepted, and with the new legislation there is now a form specifically intended for the consumers (Appendix A2).

The swiftness brought by the PortalRAM is justified by the fact that it is linked to the SVIG (*Sistema de VIGilância*), which means the data inserted in the portal are automatically available in the NPS. The SVIG is the database of the Portuguese

Pharmacovigilance System, in which are registered all the suspected ADRs reported in the system. That way, this database collects all safety information available about the use of medicinal products in Portugal. On a European level, the SVIG is connected to the EV and, at an international context, to the VigiBase.

Considering that one of the main attributions of the UFS is the management of SRs of suspected ADRs from the southern region, namely the reception, validation, analysis and processing of SRs, including the determination of the causal relationship, my training at the UFS focused mostly in these areas of the SR of ADRs by healthcare professionals and consumers.

The reports of ADRs are processed through a sequential methodology that has several phases. Next, I am going to describe in detail the procedures done at the UFS, in which I actively participate, in order to process the SRs received, from their reception and validation, going through all their processing, to the phase of causality assessment, when the causal relationship between the suspected drug and the ADR is established. The flowchart presented in Figure 6 shows, in general terms, the processing of the SRs in the UFS. For clarity purposes, this sequence is presented in its linear version, where the different steps can be followed in the indicated order.

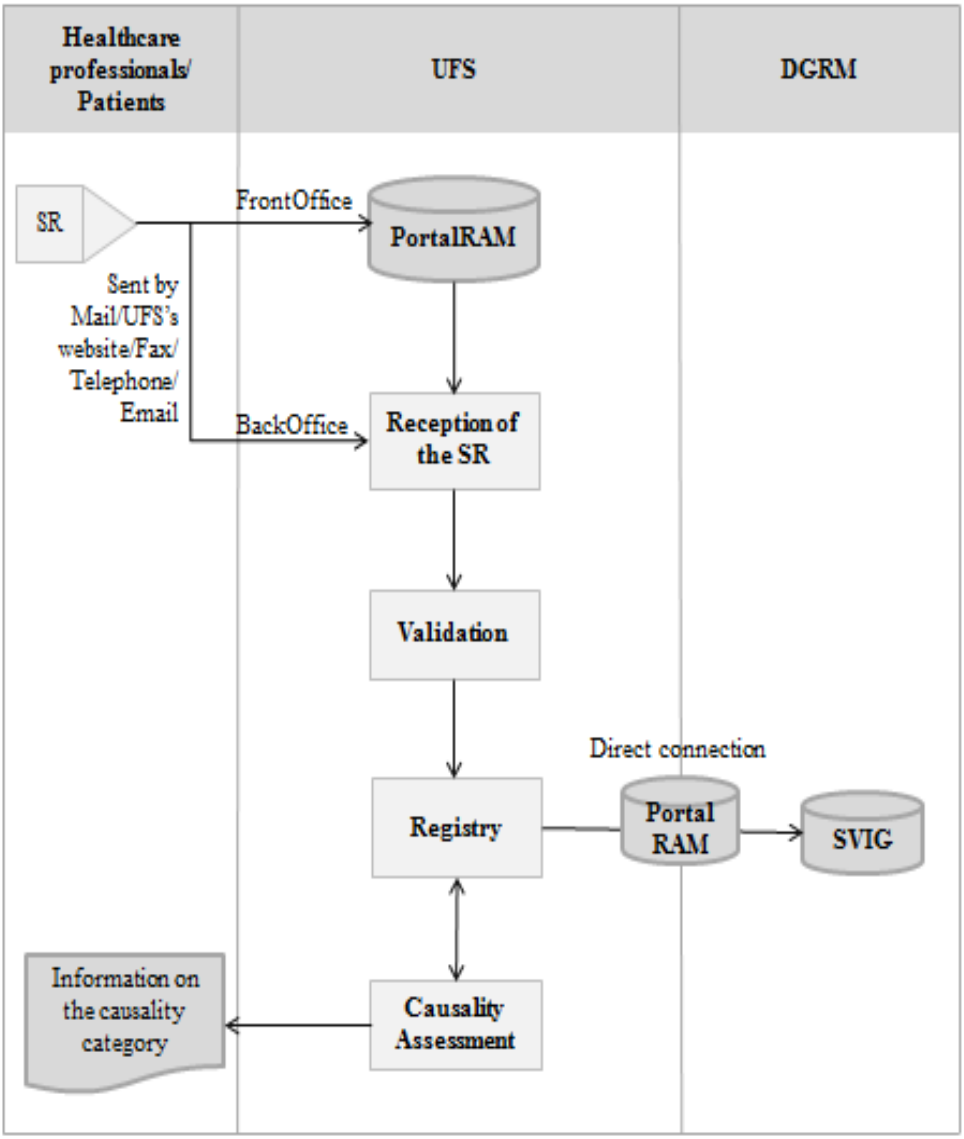

Figure 6 – Processing of the SRs in the UFS and the connection with the healthcare professionals/patients and with the DGRM

For serious ADR reports, all the process, since the reception of the SR by the RPUs until the sent by the DGRM to the EV and to the MAH(s), must be done within 15 calendar days. Therefore, each RPU has 8 days to process each SR, while the DGRM has 7 days to analyse it and to send the ADR report to the EV and to the MAH(s) of the suspected medicinal product(s).

For the non-serious ADR reports, this process must be concluded in 90 days. However, these reports are not sent to the EV, but they are only sent to the MAH(s) of the suspected medicinal product(s).

2.1.1.1 Reception and Validation of the Spontaneous Report

Figure 7 illustrates the processes of reception and validation of the SRs by the UFS and the connections with the healthcare professionals/patients and DGRM. These processes are detailed and explained bellow the flowchart.

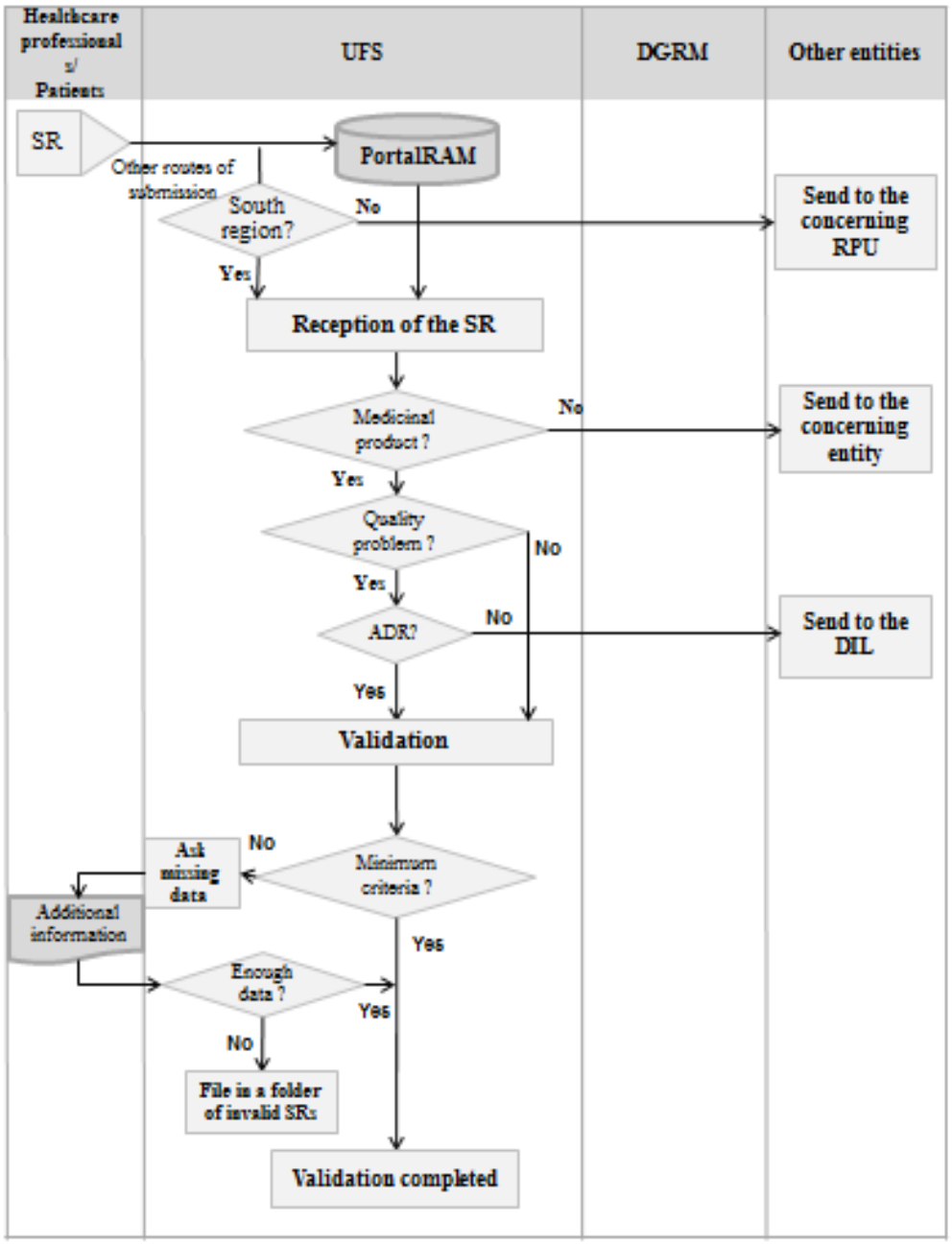

Figure 7 – Reception and validation of the SRs by the UFS and the connections with the healthcare professionals/patients and with the DGRM

Routes of Reception of SRs

Considering that the underreporting of suspected ADRs is the major drawback of the spontaneous reporting system (58), and that Portugal is, within the EU, one of the countries with the highest underreporting rate (9), all the efforts should be made to increase the number of reports. As such, and according to my experience, the UFS accepts several channels of communication for the reception of SRs of ADRs, so that each person can use the most convenient mean for them, from reporting forms on paper format to online forms. In fact, the UFS felt the need to create a tool of online reporting of ADRs, included in the website of the unit since 2008. This tool has been used a lot over the years by the healthcare professionals to report the suspected ADRs due to its easiness and quickness. Furthermore, even with the option of reporting through the PortalRAM, a lot of healthcare professionals still prefer to report through this feature of the UFS's website. Currently, there are several routes of reception of SRs at the UFS:

- PortalRAM;
- Website of the UFS;
- ADR reporting form on paper formant (sent by mail or fax);
- E-mail;
- Telephone.

All the received SRs have to be inserted in the PortalRAM, in order to be available for the other partners of the Pharmacovigilance System, both nationally and internationally. Therefore, the PortalRAM is considered a direct route of spontaneous reporting, as the reports inserted in the Portal are automatically available in the SVIG. The direct route of reporting facilitates the work done by the RPUs, since the pharmacovigilance technicians do not have to insert all the data from the received SR in the Portal. Instead, they only need to review the data inserted in the Portal by the reporters and to complete any missing data.

When a SR is reported by a healthcare professional or a consumer in the PortalRAM (submission in FrontOffice), the Portal automatically sends an e-mail to the UFS alerting for the reception of a new SR from the south region in the Portal. When a pharmacovigilance technician enters in the Portal, this SR is found with the date of its initial reception in the NPS and a submission number of the type FO-PS-YYYYMM-XX (when the reporter is a healthcare professional) or FO-U-YYYYMM-XX (when the

reporter is a consumer), in which FO means FrontOffice, PS means healthcare professional, U means consumer, YYYY and MM correspond to the year and month in which the report was introduced, respectively, and XX is a random number.

On the other hand, when the SRs are received by other routes, the collaborators of the UFS must insert in the PortalRAM all the information received (in BackOffice). The submission number of the report inserted in BackOffice (by the UFS collaborators) is also generated by the PortalRAM and has the format BO-PS-YYYYMM-XX or BO-U-YYYYMM-XX, in which BO means BackOffice, PS means healthcare professional, U means consumer, YYYY and MM correspond to the year and month in which the report was introduced, respectively, and XX is a random number.

In the cases where the SRs are not directly inserted in the PortalRAM by the reporter, it is necessary to attach the original notification in pdf format to the Portal, duly identified by its identification number, date of reception and initials of the responsible UFS collaborator. Therefore, while the SRs received in paper format must be scanned and attached to the case that will be inserted to the PortalRAM, the SRs made by the UFS's website generate an e-mail for the UFS's e-mail address that can be converted into pdf format and attached to the case in the Portal. In the cases where the SR is made by telephone, it is solicited to the reporter to submit the SR by the PortalRAM or another route. When it is not possible, the essential information should be collected by telephone and sent to the reporter by e-mail in order to receive his/her validation, so there is a written registry that may be annexed in the same way to the case in the PortalRAM. If the contact by e-mail cannot be made, then an ADR reporting form is filled, sent by mail to the reporter, soliciting his/her validation and signature.

Independently of the route of reporting, there are several steps that must be taken by the collaborators of the UFS, which are described in detail as follows.

Verifying the Reporter's Geographical Area

When the report is received by a route other than the PortalRAM, it is necessary to verify whether the reporter belongs to geographical area covered by the UFS. If the reporter belongs to the south region, the information is inserted in the PortalRAM (in BackOffice). Otherwise, the information received in the SR is sent by e-mail to the RPU responsible for the reporter's geographical area, which will process the case. Then, the SR is filed in a folder of invalid SRs.

Verifying Whether the SR is Concerning to a Medicinal Product

Another aspect that must be verified when the SR is received is whether the SR is regarding to a medicinal product for human use or it is referring to another product (for example, cosmetic, body hygiene product, food supplement, etc). For this it is made a search, in order to confirm that the product is a medicinal product. If the product is not a medicinal product, another search is made to verify the product's status and then the concerning services of the INFARMED. I.P. or the concerning entities responsible for such products are contacted (if necessary), in order to confirm it.

If the SR does not refer to a medicinal product for human use and is beyond the INFARMED's competencies, it should be sent an e-mail to the reporter indicating the contacts of the responsible entity for the product. If the SR does not refer to a medicinal product for human use but it is within the INFARMED's competencies, the SR should be sent to the concerning Department. The original SR is then filed in a folder of invalid SRs.

Verifying Whether the SR Refers to a Quality Problem of a Medicinal Product

Another thing to take into account after receiving the SR, is to verify if it is referring to a suspected quality problem. When the SR refers to a suspected quality problem without occurrence of ADR, the reporter should be informed that the SR he/she sent will be forwarded to the Inspections and Licensing Department (DIL) of the INFARMED, I.P., since there is no ADR. The DIL is the service of the INFARMED, I.P. responsible for the verification of the medicines' manufacturing conformity and by issuing quality alerts. When the SR also mentions an ADR, it should be analysed by UFS and by DIL.

Validation of the SR

At the time of the initial report, it is recommended to collect as much information as possible. However, for the purpose of regulatory reporting, in order to consider a spontaneous report valid, it has to contain certain elements, known as the minimum criteria (59-61):

- One identifiable reporter, characterised by qualification, name, initials or address. The contact details for the reporter should also be recorded in order to allow follow-up activities to be conducted. In cases where the reporter does not want to provide their contact, the case is considered valid if the organisation who was informed of the case was able to confirm it directly with the reporter;
- One single identifiable patient, characterised by at least one of the following data: name's initials, gender, date of birth, age and/or age group. This information should be as complete as possible;
- At least one suspected adverse reaction;
- At least one suspected/interaction medicinal product.

Only the reports that contain these four elements are considered valid, being qualified to be attributed an alphanumerical identifying sequence from the NPS, registered in the NPS's database and becoming an available source of safety data for signal generating. Therefore, all the reports of suspected ADRs that are received by the UFS must be validated in order to verify whether they include all the minimum criteria, making sure it qualifies as a valid case. When there is lack of any of these elements, the case is considered incomplete. However, in such cases, an effort to collect all the missing data elements is made as soon as possible, following up the case with the reporter, or with other available source. When it is not possible at all to gather the minimum information, the SR is closed and filed in a folder where all the invalid SRs are filed, electronically (if the SR was sent by e-mail or by the UFS's website) or in paper format (if the SR arrived by mail or fax). Otherwise, if the case is valid, the next step is its analysis.

When the SR arrives by another route than the PortalRAM, the minimum criteria are verified by the UFS collaborators to check if they are present before inserting any information on the case in the PortalRAM. When the SR is submitted directly in the PortalRAM by the reporter, it is necessary to open the report in the Portal, in order to verify whether the minimum criteria are present or not.

2.1.1.2 Analysis and Registry of the Spontaneous Report

The processes of analysis and registry of the SRs in the PortalRAM by the UFS and the connections with the healthcare professionals/patients and with the DGRM are presented in Figure 8. These processes are further detailed bellow the flowchart.

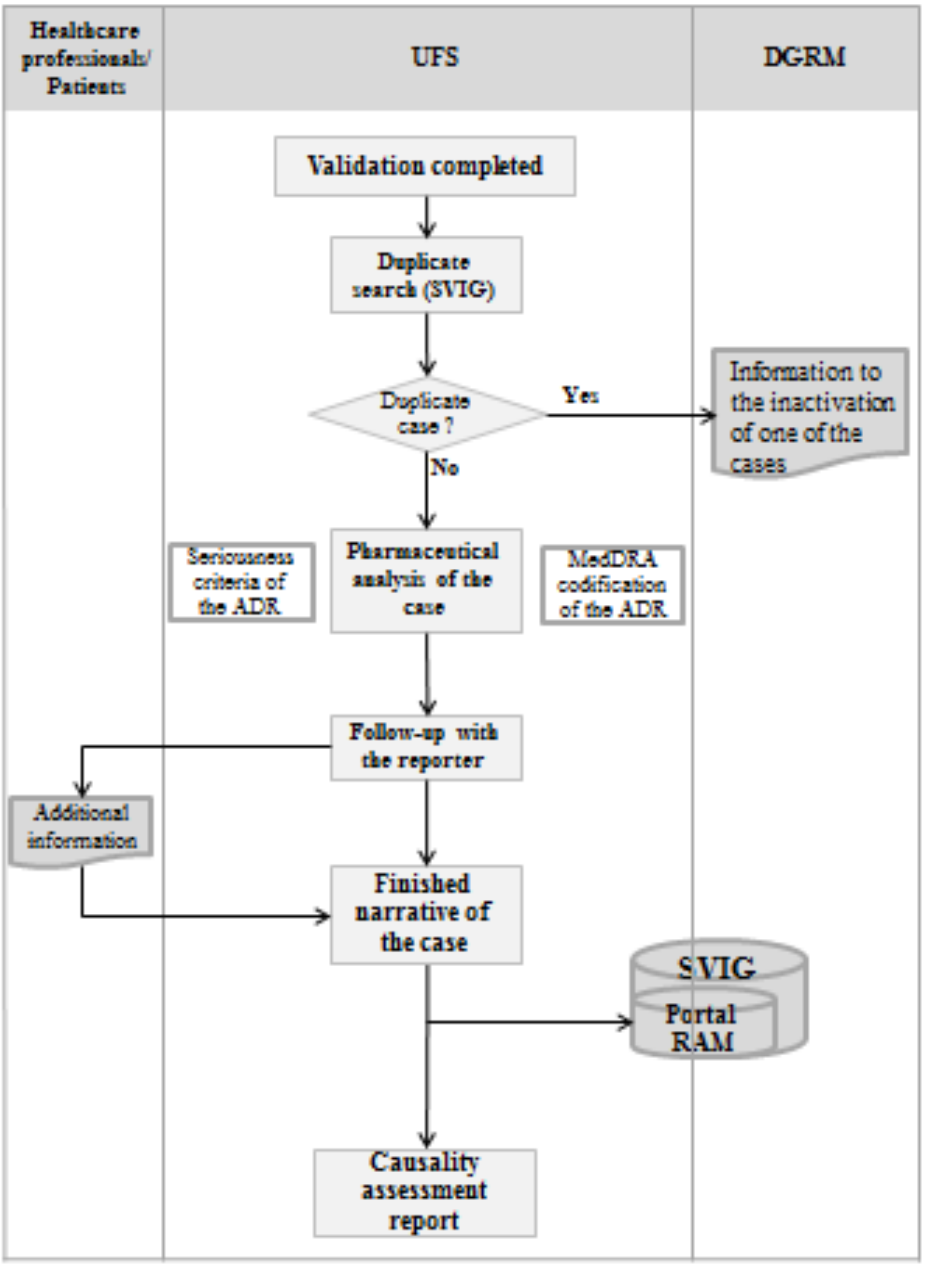

Figure 8 – Analysis and registry of the SRs by the UFS and the connections with the healthcare professionals/patients and with the DGRM

Duplicate Detection

Some suspected ADRs are reported to the authority by more than one person and/or more than one route. This gives rise to duplicate cases. The detection of such duplicates is extremely important because their presence in any pharmacovigilance database can lead to a misleading analysis of signals, potentially impacting on regulatory actions.

Therefore, after the initial validation of a SR, a duplicate detection is immediately performed through a search in the SVIG database. This search is done introducing specific data (namely information on the minimum criteria) from the received SR by the UFS in the SVIG, in order to verify whether the case is already in this database. The data introduced for the initial search are generally information from the patient, such as the name's initials, gender and/or date of birth, in order to address differences in MedDRA coding of the ADR, for example, when the cases are reported by different reporters. If these data match a case in the SVIG, then the remaining data of the case already in the SVIG must be verified in order to analyse whether it coincides with the case received. If all the fields are coincident or very similar, it may be a potential duplicate. Therefore, a follow-up has to be done with the original reporter(s) in order to request further information necessary to determine whether or not this is a duplicate. If it is confirmed that it is a duplicate, the received SR is inserted in the PortalRAM (if it was received through other route) and then inactivated. This process is important in order to account all the received SR by healthcare professionals and consumers. After this, the DGRM is informed of the situation of the duplicates via e-mail. The reporter is also informed by telephone and any new information of the case is added as follow-up information to the case that remains active in the SVIG.

In addition to this routine practice of searching for duplicates in the SVIG, there may be situations when two reports on the same case are sent by different healthcare professionals, different consumers or by a healthcare professional and a consumer, at the same time and it is necessary to manage these duplicates. In these situations, we must insert both reports in the PortalRAM (if it was received through other route), although one of them is inactivated afterwards. The criteria to select the notification to process and the one to inactivate are the following:

- Notification from a healthcare professional and from a consumer: prevails the report of the healthcare professional independently of the route it was received;
- Notification from two healthcare professionals or from two consumers:

- In the case of both being sent through the same route, the first to be received is the one that prevails;
- If the reports were sent through different routes, the report that prevails is the one send through the PortalRAM.

Although I learned how to do this, during my time at the UFS, no duplicate cases were ever found, and therefore I did not have the chance to put the knowledge I obtained on the management of duplicates into practice.

When the SR is received by a route other than the PortalRAM, the duplicates detection is made before inserting any information about the case in the Portal. When the SR is received directly by the PortalRAM, it is necessary to open it in order to verify if it is a duplicate.

After analysing the minimum criteria and conducting the duplicates detection, the PortalRAM generates a registry number and sends an e-mail to the reporter with the registry number of his/her report. This registry number consists in a sequence "SYYYYMMNNNN", in which S corresponds to the designation of the area covered by the UFS (the south), YYYY and MM to the year and month in which the report was received, respectively, and NNNN to the sequential number of valid reports received by the NPS.

Reflection on the Seriousness of the ADR

It is important to make a reflection on the seriousness of the ADR in the beginning of the SR's processing, since the SRs of serious ADRs have always priority in its processing and analysis.

Based on the judgement of the reporter (when this judgement exists), I made a clinical judgement on the seriousness of the ADRs received, alone or, when there were doubts, along with the collaborators of the UFS, according to the criteria for the classification of the ADRs' seriousness. A serious ADR is any untoward medical occurrence that at any dose (62):

- Results in death;
- Is life threatening;
- Induces inpatient hospitalisation (more than 12 h in the hospital) or prolongs an existent hospitalisation;

- Results in persistent or significant disability or incapacity (spend more than a day bed-ridden, total or partial loss of autonomy, reduction of quality of life - impact on the social and labour functioning);
- Causes a congenital anomaly/birth defect;
- Is considered medically important, that is, based on medical opinion, may jeopardise the patient or may require a clinic intervention to prevent one of the above consequences.

Medical judgement should be exercised in deciding whether other situations can be considered as serious. Several efforts have being made in order to harmonise the criteria for the classification of ADRs in serious or non-serious. Therefore, several documents have been developed for this purpose.

The Council for International Organizations for Medical Sciences (CIOMS) Working Group V suggested a list of terms that should always be considered "serious", the List of MedDRA preferred-terms to be considered "Serious" based on WHO-ART Critical Terms (63). The CIOMS is an international non-governmental organisation established in 1949 by the WHO and the United Nations Educational, Scientific and Cultural Organisation (UNESCO) that is representative of a substantial part of the biomedical scientific community. It has several work groups responsible for developing guidelines in the area of pharmacovigilance (64).

The INFARMED, I.P. also developed, in 2008, a convention in order to harmonise the seriousness criteria – Convention of Consensus Authority/Pharmacovigilance Units for the Attribution of a Criteria of Seriousness to the ADR (ConGGrav). This consensus divides the seriousness criteria in two levels: the first level contains the first seriousness categories referred above (death, life threatening, hospitalisation, disability or incapacity and congenital anomaly/birth defect) and the second level includes the conditions considered medically important, as well as the terms considered serious by the CIOMS V.

Furthermore, in order to better clarify what should be considered "medically important", the EV Expert Working Group developed a List of Important Medical Event terms based and updated on the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). This list is intended for guidance purposes and aims to facilitate the classification of suspected adverse reactions. It is available for anyone who wants to use it in the pharmacovigilance activities (59, 65). I had the opportunity to use it during my training, when I had doubts related to the seriousness of a certain ADR.

There are cases where the classification "serious" or "non-serious" may be a somewhat subjective. Sometimes the clinical expert, who is ultimately responsible for the result of the causality assessment of the cases at the UFS, changes the classification of seriousness attributed by the reporters or the collaborators of the UFS. Therefore, the consideration of what is serious and non-serious may still vary between different individuals, despite all the efforts that have been developed in the harmonisation of the criteria for this classification.

MedDRA Codification of the ADR

In order to allow the analysis and exchange of pharmacovigilance information, this information must be encoded into a common and harmonised language. For that, several dictionaries of medical terminology have been created and used in pharmacovigilance. The first dictionaries of medical terminology were developed over time, individually, by several countries, in the context of their specific needs. More recently, the need to create a unique and universally accepted dictionary arose, as a way of assuring the viability of the circulation of information among the several individual pharmacovigilance systems, which, in turn, was in the beginning of the creation of the MedDRA. This terminology was initially implemented in 1999, by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), with the aim to standardise the medical terminology used for regulatory purposes, and to facilitate the electronic communication for the transfer of this information at an international level (66, 67). The MedDRA terminology allows, therefore, the standardisation and harmonisation of the system of ADRs' classification, facilitating the exchange and analysis of safety data of the medicinal products between the regulatory authorities and pharmaceutical industry (68).

The MedDRA dictionary encodes diseases, therapeutic indications, signs and symptoms, diagnosis, medical and surgical procedures, as well as medical, familiar and social history (66). Its hierarchical structure is made up by five levels, from the most comprehensive group to the most specific: System Organ Class (SOC); High Level Group Term (HLGT); High Level Term (HLT); Preferred Term (PT), and Lowest Level Term (LLT). The most comprehensive term includes a group of more specific terms that are linked to it (66). Each MedDRA term corresponds to a numerical code of eight unique and meaningless digits, through which the transmission and exchange of

information is done (66). The MedDRA terminology can be found currently in a series of translations from the official version in English, in order to facilitate its implementation and correct use (67).

All the ADRs must be codified with a MedDRA term. Therefore, after validation and exclusion of duplicates, it is important to observe and analyse the ADR reported in order to assign it a MedDRA code.

When the reporter sends the case by the PortalRAM, occasionally he/she inserts the MedDRA code that he/she considered more appropriate. Other times, the reporter inserts only a description of the ADR in Portuguese and it is our job at the UFS to classify it with the MedDRA code. When the case is received by other routes, we have always to encode it according to MedDRA. Sometimes it is necessary to contact the reporter in order to better understand the ADR's characteristics and allow a more adequate codification. The chosen term should be the MedDRA LLT more closely corresponding to the reaction as reported by the primary source. When a MedDRA term cannot be found, a good clinical judgment should be used to choose the MedDRA term that is closer to the original reported term (69). The MedDRA Term Selection: Points to Consider (a guidance document yearly updated) should be consulted during the adverse reaction codification. This codification should be subjected to validation by the reporter. Table 1 gives some examples of ADRs' descriptions received at the UFS, and the respective LLT I chose for each one, (based on the MedDRA Points to Consider). The explanation for these choices is given below the table.

Table 1 – MedDRA encoding: Examples of the LLT chosen in specific situations

Description of the ADR by the reporter	Chosen LLT
"Patient presents hyperglycemia after taking drug A" (Drug A is a known corticosteroid)	"Hyperglycemia steroid-induced"
"Patient with controlled hypertension had an increase in the blood pressure after taking drug B"	"Hypertension aggravated"
"A patient with Alzheimer presented an aggravation in its condition after taking drug C"	"Alzheimer's disease" + "Disease progression"
"Patient developed an allergic reaction characterised by generalised pruritic skin eruption after the administration of drug D"	"Allergic reaction" + "Rash urticaria-like"

"Patient took drug E for an off-label therapeutic indication, but no adverse reaction occurred"	"Off-label use" + "No adverse reaction"
The patient changed drug F (a branded product) by its generic, drug G, and presented progression of the disease	"Disease progression" + "Product substitution issue brand to generic"

As with the examples of drug A and B, the most specific LLT that best represents the reported ADR should always be chosen.

In cases where it is reported the aggravation/progression of a previous condition and there is not a MedDRA term that combines both the condition and its aggravation/progression, two terms should be chosen, as can be seen in the example of drug C.

When a medication error or an off-label use of a medicinal product has clinical consequences, in addition to the terms for the consequences, a term for the medication error/off-label use should also be selected, as it exemplified by the example of drug D.

In the cases where is specifically reported that does not occurred an ADR, despite occurring an exposure to the drug, the term "No adverse effect" should be selected, as presented in the example of drug E.

Moreover, when there is a change in the patient's therapeutic response involving the substitution of a generic medicinal product, besides the selection of other terms appropriated to the case, one of the following MedDRA terms must be selected: generic substitution altered therapeutic response; product substitution issue brand to generic; product substitution issue generic to brand; product substitution issue generic to generic. This can be seen in the example of the drugs F and G.

This MedDRA classification is not always easy and it frequently raises doubts. This will be discussed later on in the discussion section.

Pharmaceutical Analysis of the ADR

In this phase is made an analysis of the adverse reaction and the context in which the ADR occurred. For this, several sources are consulted, namely databases such as Micromedex 2.0, Medscape, MedicinesComplete, as well as scientific literature such as PubMed.

First of all, it is necessary to characterise the ADR as expected or unexpected for the suspected medicinal product. This is made through consultation of the suspected medicinal product's SmPC. An expected ADR is described in the SmPC in terms of nature, severity and outcome, while an unexpected ADR is not described in the SmPC (33).

Besides, the SmPC of the concomitant medications are also consulted in order to verify if they can also be considered suspected medicinal products. It is also made a search on possible interactions between different medicinal products used by the patient. Contra-indications of the medicinal products and concomitant conditions of the patient are also investigated in order to discard other possible etiology for the adverse occurrence.

Sometimes, it is also necessary to analyse the excipients of the suspected medicinal product. This is especially important in the cases where a patient substituted a medicinal product by another with the same active substance and developed an ADR to the second medicinal product, while the former medicine had never caused him any problem.

Furthermore, in this phase a narrative of the case starts to be written. The narrative is a text written by the collaborators of the UFS in an agreed format with the description of the case. It summarises all the information present in the SR and is structured in order to, right on the first sentence, include the minimum criteria (a brief summary of the case). Next, it should include information on the start and duration of the ADR, the relationship between the medicinal product and the ADR, the measure taken regarding the product, the treatment made for the ADR, the concomitant medications taken by the patient, other relevant information on the evaluation of the ADR and the evolution/outcome of the ADR, by this order. Usually, this narrative can only be concluded after establishing a contact with the reporter and will integrate the causality assessment report.

Therefore, after writing the draft of the narrative, a questionnaire for follow-up with the reporter is developed, contemplating any questions raised during the previous procedures.

Follow-up with the Reporter

The information in the reports of adverse reactions may be incomplete when received. In these cases, a follow-up with the reporter should be made in order to clarify

any unclear data or doubt derived from the pharmaceutical analysis and/or to obtain any additional information needed for the scientific evaluation of the case. In fact, in the great majority of the reports that I processed, I had to make a follow-up. The collection of missing information should be done in a way that encourages the reporter to submit the relevant information, being careful to not discourage future spontaneous reporting. Therefore, in the follow-ups that I made, I always made sure that I did not request from the reporter any information already provided in the initial report and, whenever possible, I was careful not to conduct extensive questionnaires to the reporter. In order to do so, every time I had to make a follow-up, I prepared in advance a questionnaire with simple and quick answer questions including the missing information, in a follow-up form. The follow-ups I made were mostly done through telephone, since the reporters do not always reply to the e-mails that we send. It is important that this phone call be brief, to avoid bothering the reporter and always thank them for the report, as a way of encouraging them for future reports. During the phone call, any new information from the case given by the reporter is written in the follow-up form, which is, after the conclusion of the case, annexed to the causality assessment report. Occasionally, this contact with the reporters was made through a questionnaire sent by e-mail, which was later printed, along with the reporter's answers, to be annexed to the causality assessment report.

In the USF, an attempt is made to contact the reporter in the day of the reception of the SR. When it is not possible to establish this contact in the day of the reception, all the efforts are made to establish this contact as soon as possible.

After the follow-up with the reporter, the narrative of the case can be finished with the new information and inserted in the PortalRAM.

Registry of the SR in the PortalRAM

As I mentioned before, when the report is sent to the UFS directly by the PortalRAM (FrontOffice), the UFS collaborators have only to analyse it, detect and correct some possible mistakes and complete the missing fields. When the report is sent by other routes, on the contrary, the UFS collaborators have to insert all the information reported in the PortalRAM (BackOffice). For that, after opening the PortalRAM, the menu "report reaction" is selected. Then, one of the options "healthcare professional" or

"patient" is selected, whether the concerned report was made by a healthcare professional or by a patient (Figure 9).

Figure 9 – PortalRAM: Start of the insertion of a SR, in BackOffice.

After this, the several menus presented (Adverse Reaction Menu; Medicinal Product Menu; Patient Menu; Other Information Menu; Reporter Menu; Administrative Data Menu; Management of the SR Menu) start to be filled, in any order.

At the UFS an effort is made to fulfil all the fields of the several menus presented in the PortalRAM, although it is not always possible since not all information is available.

However, that are several fields that are mandatory to be filled, otherwise the report is not sent to the SVIG. The mandatory fields are marked by an asterisk in the PortalRAM and it can be seen in the following images outputs presented in this section to describe the functionalities of the PortalRAM.

Next, I am going to detail the information that should be inserted in each menu for each report received.

In the **Adverse Reaction Menu**, the following information should be inserted (Figure 10):

- The MedDRA term of the ADR(s) reported and its(their) description (when considered relevant);
- The dates in which the patient started and stopped using the suspected medicinal product;
- The seriousness of the ADR(s) and, when classified as serious, the justification for this assumption;
- The expectedness of the adverse reaction(s), that is, whether the ADR(s) is(are) listed or not in the SmPC;

- Whether any treatment to the ADR(s) was conducted and, if so, which one;
- The evolution of the patient's condition (cure, cure with consequences, in recovery, persists without recovery, unknown, death).

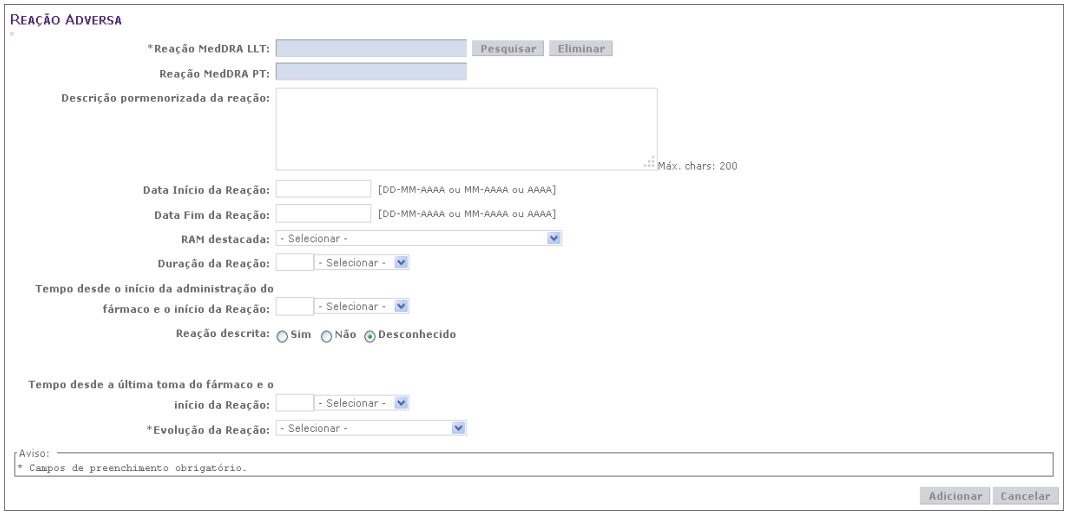

Figure 10 – PortalRAM: Adverse Reaction Menu

In the **Medicinal Product Menu**, information on the suspected medicinal product and the concomitant medication should be inserted[5]. For each medicinal product is requested information on:

- Whether the drug is considered suspect of causing the ADR, is a concomitant medication or an interaction;
- Its brand name (Figure 11) or, when it is not possible to obtain this information, the active substance along with the Anatomical Therapeutic Chemical (ATC) classification[6] (70) (Figure 12);
- The batch of the medicinal product;
- The therapeutic indication, encoded with the correct MedDRA code;
- Its route of administration and administration site;

[5] Concomitant medication: Any medicinal product that is not suspected of causing the ADR and is administered to the patient at the time of the reaction reported.

[6] The Anatomical Therapeutic Chemical (ATC) classification system divides the active substances into several groups according to the organ or system on which they act, as well as their therapeutic, pharmacological and chemical properties. This is one of the most used systems to classify molecules with therapeutic action.

- The start date and end date (if applicable) of the treatment with the medicinal product;
- Whether it was the first use of the medicinal product or if it had been used previously by the patient;
- The temporal relationship between the drug and the beginning of the ADR;
- Its dose and posology;
- The measure taken to the medicinal product (suspended, increased dose, decreased dose, unchanged dose, unknown or not applicable) and the evolution of the patient after measure taken and after the re-introduction of the medicinal product, if applicable.

In this menu there is also a section to insert the opinions of the reporter and regulatory authority (the UFS in this case) on the causal relationship of the suspected medicinal product with the ADR. The space for the reporter's opinion may be filled after making a follow-up with him/her. However, the section of the UFS' opinion on the causal relationship can only be filled afterwards, when the case is discussed with the clinical expert, as will be detailed later in this report.

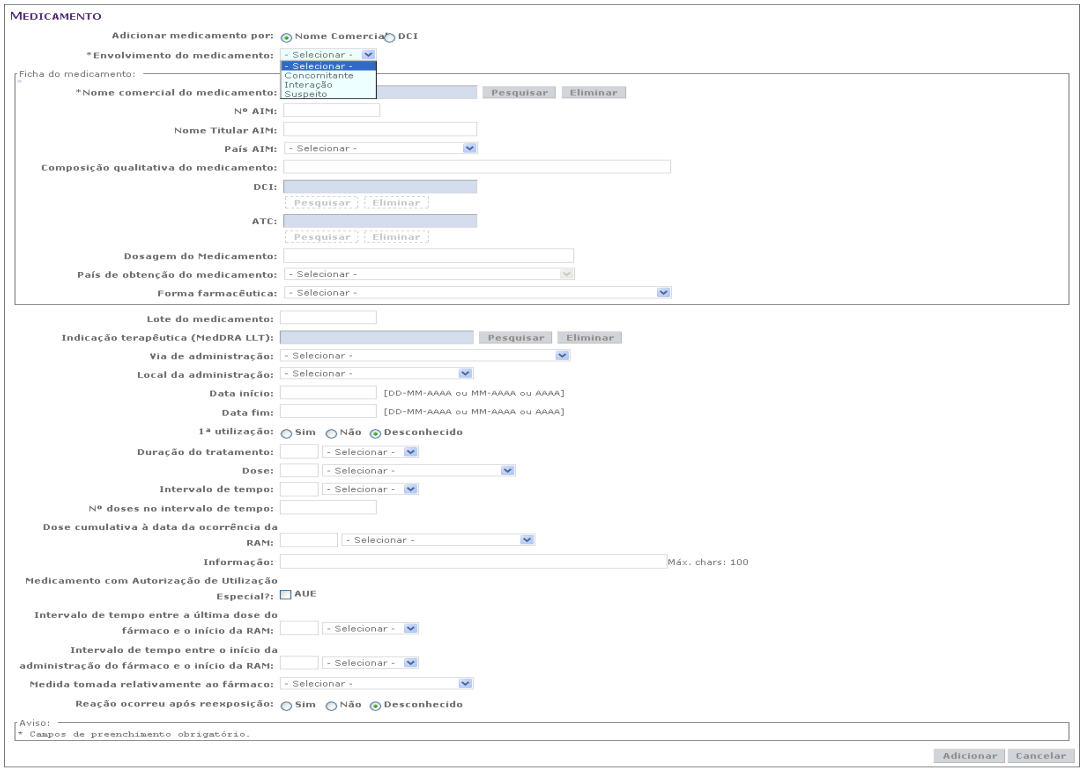

Figure 11 – PortalRAM: Medicinal Product Menu when the brand name is known

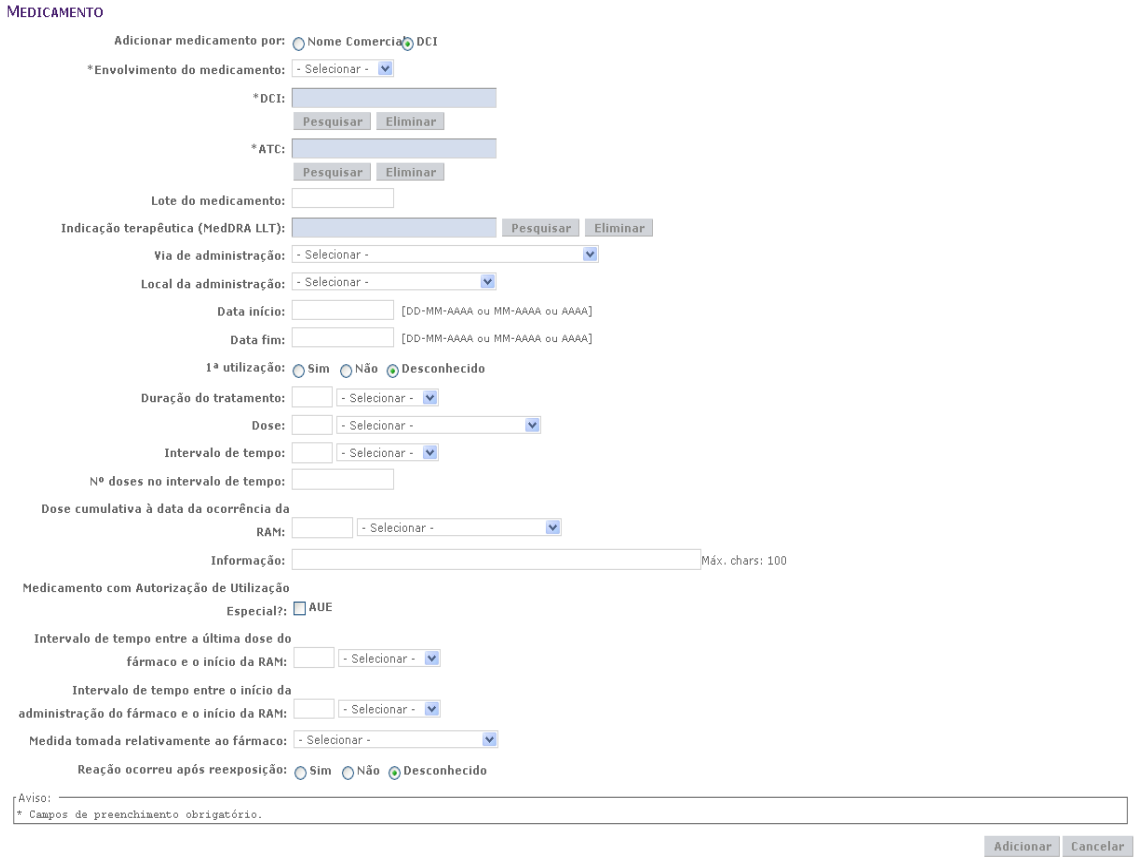

Figure 12 – PortalRAM: Medicinal Product Menu when the brand name is not known

The **Patient Menu** (Figure 13) presents the following sub-menus: Patient Data, Clinical History, Pharmacological History, Tests, Death and Parent Data.

The **Patient Data sub-menu** includes the following information:

- Name's initials, gender and birth date;
- Weight and height;
- The evolution of the patient's condition (cure, cure with consequences, in recovery, persists without recovery, unknown, death);
- Whether the patient is hospitalised or not.

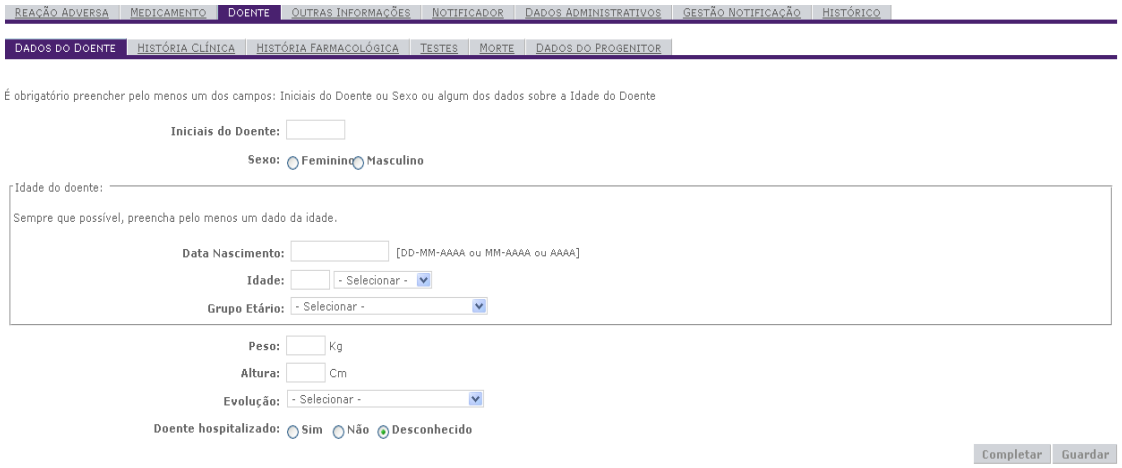

Figure 13 – PortalRAM: Patient Menu

The **Clinical History sub-menu** includes the patient's current and previous pathologies, encoded with the respective MedDRA terms.

In the **Pharmacological History sub-menu** should be inserted the patient's past drug therapy, that is, any medicine that was discontinued before the start of the treatment with the suspected medicinal product.

In the **Tests sub-menu** are inserted the laboratory tests performed to the patient, encoded in MedDRA, the date in which they were conducted and their results.

The **Death sub-menu** is only filled if the patient has died and includes the date of death and whether an autopsy was done or not.

The **Parent Data sub-menu** contains information on the parent, such as its name's initials, gender, age, date of birth, as well as its relevant clinical and pharmacological history, encoded in MedDRA (Figure 14).

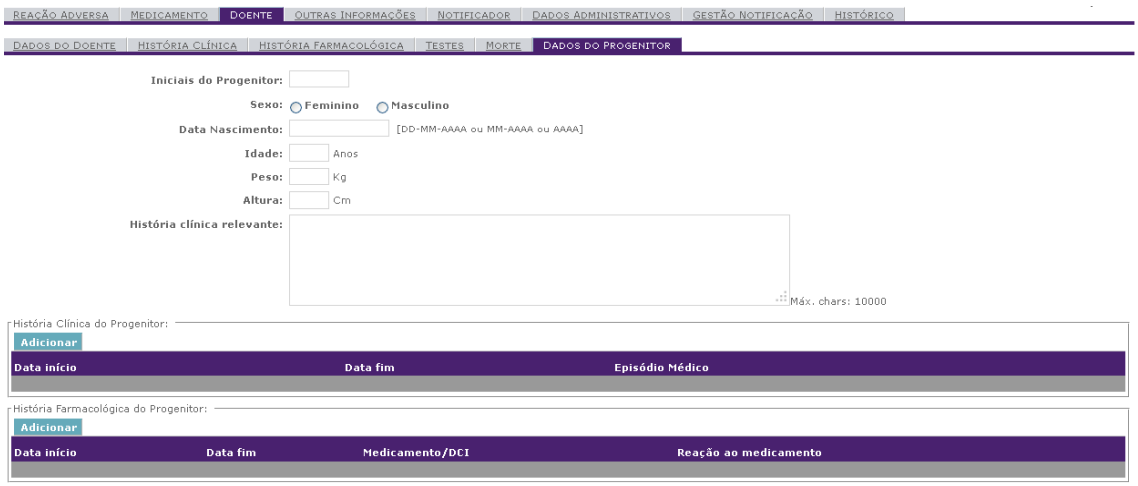

Figure 14 – PortalRAM: Parent Data sub-menu

The **Other Information Menu** includes free writing spaces where any additional information given by the reporter may be inserted, as well as the narrative of the case. The narrative, generally, summarises the information inserted on the PortalRAM.

In the **Reporter Menu** is inserted information on the primary source, that is, the person who reported the suspected ADR to the UFS, such as the reporter's name, contact (e-mail and telephone number), professional category and institution where he/she works (Figure 15). This e-mail address is important, since the PortalRAM automatically sends an e-mail to the reporter warning that its report was inserted in the Portal.

Figure 15 – PortalRAM: Reporter Menu

In the **Administrative Data Menu,** the following information is required:

- Date in which the reporter was made aware of the case (this field can only be filled after contacting the reporter);
- Date of the reception of the initial case in the PortalRAM;
- Date of the most recent information inserted in the PortalRAM;
- The state of the report (evaluated, in evaluation, in re-evaluation, incomplete);
- Country of the reporter.

Besides, in this menu, is also necessary to select whether the case fulfil the criteria for an expedited report or not.

In the **Management of the Report Menu**, it is requested information on the dates of the reception of the SR and finalisation of the analysis of the case.

When all the menus of the PortalRAM are filled and reviewed, including the information gathered in the follow-up with the reporter and the final narrative inserted, the information present in the PortalRAM is automatically sent to the SVIG. The SR remains visible in the portal, since the causality assessment was not done yet and the opinion on the causal relationship between the suspect drug and the ADR was not inserted. Only after the meeting with the clinical expert to discuss the causal relationship attributed to the case is it possible to conclude the report in the Portal.

2.1.1.3 Causality Assessment

The processes involved in the causality assessment of the SRs in the UFS and the connections with the healthcare professionals/patients and with the DGRM are presented in Figure 16. These processes are fully explained bellow the figure.

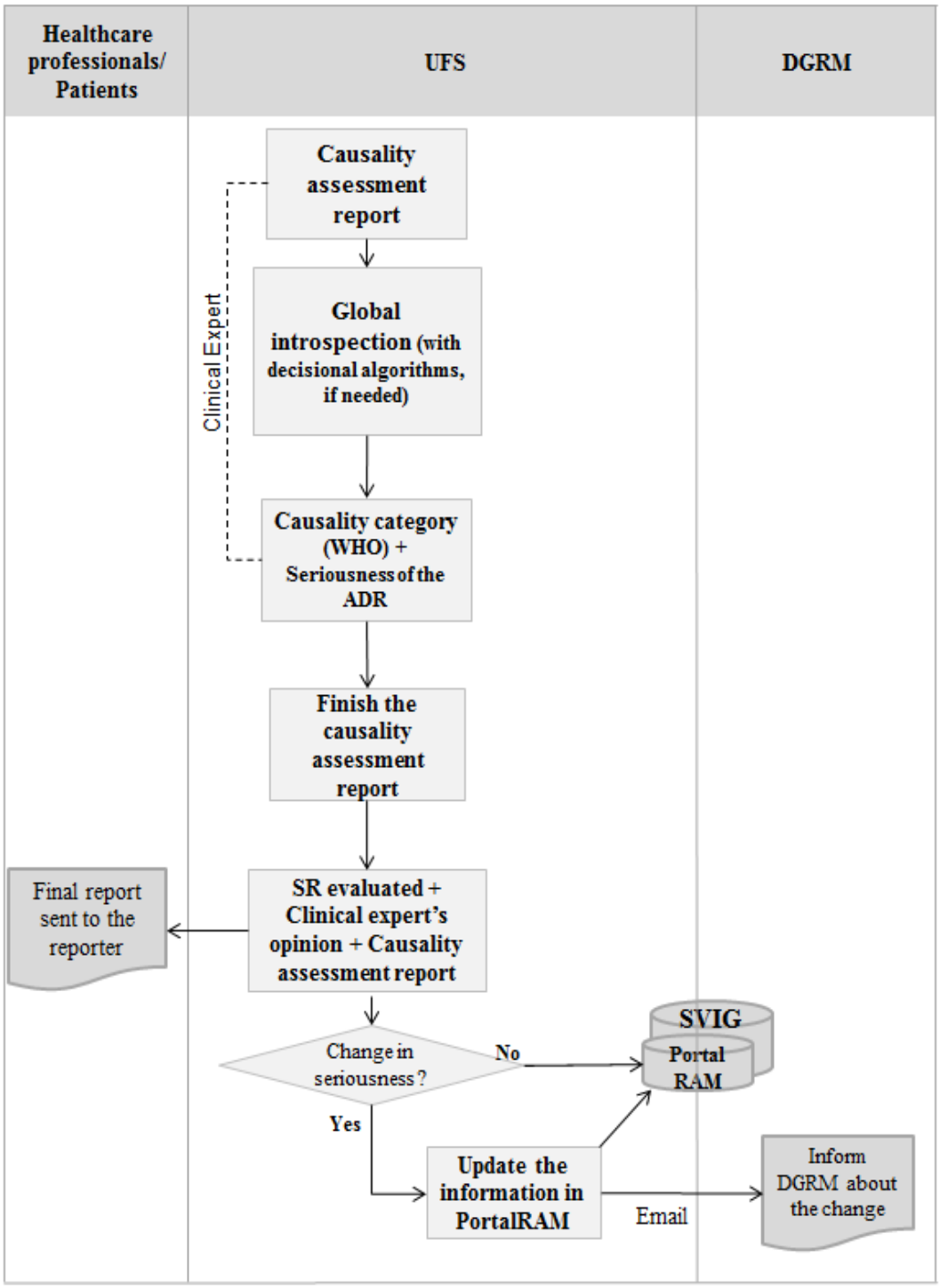

Figure 16 – Causality assessment of the SRs by the UFS and the connections with the healthcare professionals/patients and with the DGRM

Elaboration of the Causality Assessment Report

The collaborators of the UFS develop a report for all the received SRs with the data from the case and the respective causality assessment. This report includes the following information:

- Information on the reporter;
- Narrative of the case;
- MedDRA term(s) and seriousness of the ADR(s);
- Relevant information found during the pharmaceutical analysis of the case, such as information contained in the SmPCs of the suspected medicinal product(s) and concomitant medication and in other relevant sources;
- Causality assessment (global introspection method and Naranjo's algorithm);
- Provisory causality category to be attributed by the UFS;
- Final causality category to be attributed by the clinical expert and his signature;

Most of the times, I started to elaborate the report on the same day of the reception of the SR, or no later than the day after. When it is complete, it is printed and filed on a folder along with other cases that wait the meeting with the clinical expert to discuss their causality assessment.

Attribution of a Causality Category

This phase is extremely important and is considered the pillar of all the pharmacovigilance systems, since the reliability of the data used in regulation and the wide use of drugs by the population is dependent on this process (71).

According to the Directive 2010/84/EU of 15 December 2012, the concept of ADR includes the existence of at least a reasonable possibility of a causal relationship between a medicinal product and an adverse event (33).

Causality assessment is the evaluation of the likelihood of a medicinal product being responsible for causing an adverse reaction. This process results on the attribution of a causal relationship between the use of a medicinal product and the adverse occurrence. During this process, there are two questions that should be answered: "may the medicinal product cause the described adverse reaction?" and "the medicinal product caused this adverse reaction?" (71).

When evaluating the responsibility of a medicinal product on the origin of an adverse reaction, it is extremely important to analyse all the intervenient variables in this process in order to avoid a biased evaluation, namely the suspected medicinal product, the individual to whom it was administered, and any other variables that may interfere with the administration of the medicinal product on the individual. However, assessing causality is a complex and difficult process and there is not a satisfactory model for doing so. In fact, it always ends up including a certain degree of subjectivity from the assessor. As a way to reduce such subjectivity, pharmacovigilance systems have been using different methodologies in this evaluation. The most used model in assessing causality is the WHO global introspection method, which takes into account the ADR and the medicinal product profile, as well as the overall context in which the ADR occurred (71). This is the standard method used in the UFS, and I used it in all causality assessments that I made. The global introspection method is based on the following considerations (71, 72):

- The temporal relationship between taking the medicinal product and the onset of the event;
- The medical or pharmacological plausibility (signs and symptoms, laboratory tests, pathological findings and mechanism of action);
- The evolution of the event after suspension of the medicinal product (dechallenge);
- The result of the re-administration of the medicine to the patient (rechallenge);
- Other possible causes (concomitant medications and diseases);
- The current knowledge of nature and frequency of the adverse reactions (similar ADRs already recognised for the medicinal product, high frequency of reports, etc).

Most of these questions can be answered with the information contained in the SR and in the follow-up with the reporter. However, it is always necessary to perform a search in the medical literature, databases and SmPCs, to find any ADRs similar to the one reported, either in clinical trials, or in data from post-authorisation use.

Besides global introspection method, there are other methods to assess causality, such as the Naranjo's algorithm, created with the aim of reducing the fallibility of human judgement and inconsistency inevitable in the global introspection method. This

method, designed by Naranjo et al., consists in a questionnaire to assign probability scores for determining the likelihood of a medicinal product causing an ADR. This questionnaire has 10 questions that are answered as Yes, No, or Do not know. Different scores are assigned to each answer (Table 2). The total score, calculated from these questions, defines the category to which an ADR belongs to. Therefore, the causality category is certain when the total score is superior to 8, probable when the score is between 5 and 8, possible when it is between 1 and 4 and unlikely when the score is less than 1 (72, 73). The Naranjo's algorithm is considered a good instrument for harmonisation purposes in investigation projects of pharmacovigilance (72).

Table 2 – Naranjo's Algorithm

Question	Yes	No	Do not Know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0
Total Score			

During the last two months of training at the UFS we decided to include the Naranjo's algorithm as well, in the causality assessment, in order to see whether the results of this method differ from those of the global introspection. However, my final decisions on the causality category of the cases were always based on the global introspection method, since the probabilistic models like the Naranjo are considered weak tools for being used in the current practice and so they should be used only as

complement to the global introspection method, when the latter raises any question. In fact, in the Naranjo's algorithm, when there are some data that are unavailable, it is attributed a "zero", which may create a bias and originate misleading results. Consequently, the result of the causality assessment in the UFS is always based on the global introspection model.

Relatively to the causality categories, the NPS uses the terminology proposed by the WHO-UMC: certain, probable, possible, unlikely, conditional/unclassified, unassessable (Table 3) (74).

Table 3 – Causality categories described by the WHO-UMC

Causality category	Description
Certain	A clinical event or laboratory test abnormality that occurred with a plausible temporal relation to the administration of a medicinal product, and it cannot be explained by any concomitant diseases or other medicinal products. The response to withdrawal of the drug (dechallenge) is clinically plausible. The event must be definitive from a pharmacological or phenomenological point of view, using a satisfactory rechallenge procedure if necessary.
Probable	A clinical event or laboratory test abnormality, with a reasonable time sequence to the administration of the medicinal product, unlikely to be caused by other conditions or other medicinal products, and which follows a clinically reasonable response on withdrawal (dechallenge). In order to fulfil this category, rechallenge information is not required.
Possible	A clinical event or laboratory test abnormality, with a reasonable time sequence to the medicine intake, but can also be explained by other conditions or other medicinal products. Information on the patient evolution after the product has been withdrawn may not be available or is unclear.
Unlikely	A clinical event or laboratory test abnormality, with a temporal relationship to the medicinal product administration which makes a causal relationship improbable (but not impossible), and in which other conditions or medicinal products provide plausible explanations.
Conditional/ Unclassified	A clinical event or laboratory test abnormality reported as an adverse reaction, about which more information is essential to properly evaluate the case, or that the additional information is under examination.
Unassessable	A report suggesting an adverse reaction but which cannot be judged because the information is insufficient or contradictory and cannot be confirmed.

Although I have always done causality assessments for all the SRs I processed, the final decision in the causality category is given by a clinical expert (a physician from the *Hospital de Santa Maria*) responsible for the causality assessments in the UFS. Therefore, every 15 days there was a meeting between the UFS and the clinical expert in order to discuss the assessment of the cases. At this meeting, the clinical expert analyses and reviews the report. His evaluation focus on the following aspects:

- Validation of the MedDRA codification;
- Validation of the seriousness of the case;
- Validation of the classification of the ADR(s) in expected/unexpected;
- Attribution of a causality category between the suspected medicinal product(s) and the ADR(s).

For this, the case is discussed with the collaborators of the UFS and finally the clinical expert gives a causality category for each ADR, together with a justification for its choice, when applicable. I had the opportunity to discuss the causal relationship to be attributed to the cases with the clinical expert.

After these meetings, there are several steps that must be taken for every case evaluated, as soon as possible:

1st - To complete the causality assessment report in word format for each case evaluated, by adding the causality category given by the clinical expert and the date of this evaluation, just like any other changes that he had done in the report.

2nd - To open each case in the PortalRAM and add the final opinion of the clinical expert on the causal relationship for each suspected medicinal product, attach to the case in the PortalRAM the causality assessment report in pdf format and update the "date of the most recent information". Finally, this information is sent to the SVIG.

3rd - To send an e-mail to each one of the reporters, with the causality assessment report(s) of the case(s) sent by each of them, including the result of the causality assessment given to the case(s), as well as all the process of global introspection that led to the attribution of that causal relationship.

Sometimes, the clinical expert changes a MedDRA term or changes the seriousness of some of the cases, both from serious to non-serious or from non-serious to serious. When that happens, or when there are posterior follow-ups with relevant information, additional steps are added to the ones mentioned above:

- Update the causality assessment report with the new information;

- Change the respective fields of the case in the PortalRAM, add the new information to the narrative, with the designation of “follow-up” with the date of the follow-up, and update the “date of the most recent information”;
- Send an e-mail to the DGRM with the follow-up information.

Concluded Cases:

The SR for which all the required and available information has been collected and has a causality category attributed, or that, despite all the data that can be collected, it is still impossible to conduct a causality assessment, is considered a concluded case.

Finally, an internal database where all the cases received by the UFS are registered is updated with the information of the concluded case, and the printed causality assessment report signed by the clinical expert is filed in a folder along with all the other concluded cases.

2.1.2 Analysis Reports on Potential Safety and Quality Signals

Regularly, I and the two collaborators of the UFS gathered to detect possible safety or quality signals. This were done through the analysis of the internal database where all the SRs received by the UFS are registered in order to see whether there is several similar reactions to the same medicinal product or other abnormal situation (for example a serious unexpected reaction) that could raise a potential safety or quality signal. The potential signals that were found resulted in a report on potential safety or quality signal, which were sent to the DGRM, for evaluation. These reports summarise the SRs that triggered the potential signal and contain all the gathered information that supports the suspicion. It is also usual to contact the reporter of the concerned cases in order to ask for specific information, such as the conservation conditions or the administration details of the medicinal product. The answers of the reporters are also included in these reports. More specifically, the structure of these reports is the following:

- An introduction, where it is made a characterisation of the suspected medicinal product (such as its therapeutic class, therapeutic indications, mechanism of action, active substance, excipients, etc), a characterisation of the concerned

ADR and a literature review regarding other cases of that ADR with the use of the suspected medicinal product concerned;

- The number of similar cases found in the UFS database in a certain period of time and a summary of the concerned SRs, including any additional information given by the reporter;
- Whether the ADR is expected or unexpected for that medicinal product, based on the SmPC, Micromedex, or other reference databases;
- A discussion on the case and conclusion.

This process of analysis of the internal database and search for possible signals is made almost in an empiric way, without much rigor. Furthermore, it is a slow process. It is only possible to do it this way because the number of cases in the database is relatively small, otherwise it would not be possible. Therefore, it is necessary to develop efficient means for detection of safety and quality signals, such as a computer programme that alerts for the possible existence of a signal.

2.1.3 Biannual Report

As stated in the Decree-Law 176/2006, the RPUs have to elaborate and present the result of the activities performed during each semester to the INFARMED, I.P. (27). I had the opportunity to participate in the elaboration of the report of the UFS corresponding to the 2nd semester of 2012, counting, for this semester, the number of SRs received by the UFS, the number of serious and non-serious reports, the number of training courses, the number of analysis reports on possible safety/quality signals, and so on. This report describes the activities developed by the UFS during one semester, with a score being given for the global execution rate of the objectives and deadlines related to the activities to be developed by the UFS, so that the unit can be evaluated. For this, essentially thirteen indicators are evaluated, related to the activities of processing and analysis of ADRs, divulgation and promotion of the system and specific communication with the INFARMED, I.P.. Through the analysis of Table 4, it is possible to verify that the UFS obtained a score of 100% on all the indicators, except the indicators relative to the rate of serious and/or unexpected ADRs, the average time of causality assessment and the emission rate of analysis reports on possible safety signals.

Table 4 – Indicators presented in the Biannual Report and the corresponding achievement for each indicator by the UFS

Indicators	Objective	Achievement
ADRs report rate	≥75/Semester	100%
Rate of serious and/or unexpected ADRs	≥70%	62%
Rate of responses to the reporter	100%	100%
Rate of ADRs with attributed causality assessment	100%	100%
Average time of the initial response to the reporter	≤ 48h	100%
Average time of causality assessment	≤15 days	83%
Emission rate of analysis reports on possible safety signals	100%	25%
Emission rate of analysis reports on possible quality signals	100%	100%
Number of training courses done	≥ 2/Semester	100%
Number of activities of divulgation	≥ 6/Semester	100%
Average upload time of the ADR report onto the SVIG	5 days	100%
Rate of urgent communication	100%	100%

The biannual report must be sent to the INFARMED, I.P. until the day 14 of the following month after the end of the semester, which corresponds to January 14th and July 14th.

2.1.4 Pharmacovigilance Training in Grândola

As already mentioned, one of the responsibilities of the RPUs is to promote the SRs of suspected ADRs in their geographical area and to organise trainings in pharmacovigilance. These trainings should be performed regularly, since as time passes, people forget what they were taught in trainings. I had the opportunity to participate in one of this trainings in *Centro de Saúde de* Grândola, for physicians and nurses. Grândola is one of the municipalities of Setúbal district that are a part of the geographical area covered by the UFS. Although I did not give the presentation, I attended it and assisted in its organisation and in the elaboration of the presentation in PowerPoint format.

2.1.5 Other Specific Activities at the Southern Regional Pharmacovigilance Unit

On the first days of my curricular training at the UFS, I was asked to read an article "The pharmacovigilance system in Portugal (its creation and development)" (75) and one chapter of the book "Pharmacovigilance in Portugal", about the "Historical Aspects of Pharmacovigilance" (11) and to summarise it. I consider it was a good way to start my training, since it allowed me to deepen my knowledge about the creation of pharmacovigilance in Portugal.

I was also asked to read and summarise the collaboration protocol between the UFS and the INFARMED, I.P..

Another activity that was proposed for me to do was to list the differences between the Spontaneous ADR Reporting Form for healthcare professionals and for patients. These two reporting forms are similar, but there are some differences between them. For example, the reporting form for the patients has a more simple language and more specific questions. Besides, some information in the patients' reporting form is explained into brackets. Moreover, in both reporting forms there is a field with instructions for filling, although the content of it is different in each reporting form, taking into account the level of knowledge of their different recipients.

It was also required for me to elaborate a possible programme for a course on the new pharmacovigilance legislation to be organised by the FFUL.

2.2 Activities Developed at the Risk Management for Medicines Department

This section describes the main and tasks developed during my curricular training at the DGRM of the INFARMED, I.P..

2.2.1 Safety Monitoring of Medicines

CAs and MAHs should take the appropriate measures to collect the suspected ADRs, either from unsolicited or solicited sources. For this purpose, a pharmacovigilance system should be created. This system should allow the validation and exchange of the reports of suspected ADRs between CAs and MAHs within the appropriate reporting time frame (59).

During the post-authorisation phase, there are two types of safety reports: reports from unsolicited sources and from solicited sources (59).

A spontaneous report is an unsolicited communication by a healthcare professional or consumer to a CA, MAH or other organisation as a Regional Pharmacovigilance Centre that describes one or more suspected ADRs in a patient who was given one or more medicinal products and that does not derive from any study or organised data collection system where the reporting of ADRs is actively sought. MAHs shall record all reports of suspected ADRs originating from within or outside the EU, which are brought to their attention spontaneously (by healthcare professionals or consumers) (59).

If a MAH becomes aware of a report of suspected ADR originating from a non-medical source, for example the lay press, internet or digital media, it should be handled as a SR, therefore making it an unsolicited report (59).

Other type of unsolicited reports is those reports of suspected ADRs from the scientific and medical literature. These reports should be reviewed and evaluated by the MAHs to identify and record ICSRs resulting from SRs or non-interventional post-authorisation studies. The scientific and medical literature provides important information concerning the monitoring of the safety profile and of the risk-benefit balance of the medicinal products. Therefore, MAHs should conduct a systemic literature review of reference databases, at least once a week, for all active substances of their medicinal products with MA. One case should be created for each single patient identifiable in the article, the relevant medical information should be provided and the publication author should be considered the primary source. Articles can be excluded from the reporting of ICSRs by the MAH if another company's branded medicinal product is clearly the suspected medicinal product (59).

Solicited reports of suspected ADRs are those that cannot be considered spontaneous and may be derived from organised data collection systems, including

clinical trials, non-interventional studies, registries, patient support and disease management programmes, surveys of patients or healthcare providers, and others. MAHs shall record all reports of suspected ADRs resulting from within or outside the EU, which occur in post-authorisation studies, initiated, managed, or financed by them (59).

The activities I developed during my training in DGRM were mainly related with the reception, analysis and evaluation of the ADR reports sent by the MAHs.

2.2.1.1 Electronic Transmission

Most ICSRs exchanged between the DGRM and the MAHs are sent by electronic transmission, a safe, fast and effective way of transmitting information, according to international agreed standards. The electronic transmission of ICSRs between the MAHs/Sponsors of Clinical Trials, National CAs and the EMA is a mandatory requirement according to the Regulation No 726/2004 and the Directive 2001/83/EC. The INFARMED, I.P. was the first CA of the UE to establish the electronic transmission of pharmacovigilance information with the EMA.

All the ICSRs in electronic transmission are identified by a worldwide identification (WWID) number. The WWID is a unique number that identifies a single case and all its follow-ups. The data elements for transmission of ICSR are detailed in the ICH guideline E2B (R2): Data Elements for transmission of individual case safety reports. The data elements are divided into section A and section B:

- A. Administrative and Identification Information
    - A.1. Identification of the case safety report
    - A.2. Primary source(s) of information
    - A.3. Information on sender and receiver of case safety report
- B. Information on the case
    - B.1. Patient characteristics
    - B.2. Reaction(s)/event(s)
    - B.3. Results of tests and procedures relevant to the investigation of the patient
    - B.4. Drug(s) information
    - B.5. Narrative case summary and further information

Each section is identified by a letter (A or B) followed by numbers, which correspond to the sub-sections. The ICH guideline E2B describes what should be present in each section and sub-section.

The safety messages in electronic transmission are sent in Extensible Mark-up Language (XML) files. These files may contain one or several ICSRs.

When a safety message is sent, there is a confirmation of the reception of the information by the receiver to the sender, with the generation of an acknowledgement (ACK) report. When the receiver processes the safety message, he/she sends an ACK report to the sender informing whether the report was accepted or not.

There are three transmission ACK codes: ACK 01, ACK 02 and ACK 03. The ACK 01 means the ICSR does not contain any errors and, consequently, the safety reports are loaded; the ACK 02 means the ICSR contains errors and, consequently, not all safety reports are loaded; the ACK 03 means there was a message or system error and no data can be extracted from the safety message received.

2.2.1.2 Adverse Drug Reaction Database – SVIG

The SVIG is the database of the Portuguese Pharmacovigilance System developed by the INFARMED, I.P. in 2004, in which the suspected ADRs reported in the System are registered. This database allows not only the manual insertion of the ICSRs, but also their electronic reception. The sections of the SVIG are based on the ICH Guideline E2B and the most important ones for ensuring the quality of the ICSRs are described next.

Administrative information Menu: This section comprises information referring to the identification of the case, namely the INFARMED's number, company's number and safety report ID, the dates of the initial and most recent reception of information by the primary source and inserted in the sector, the state (active or inactive) and type (spontaneous, study or other) of the report, the country of the reporter and where the ADR occurred, information on whether the case has medical confirmation or not and the seriousness of the case.

Annexes Menu: This section contains the documents related with the report, as well as the identification of the related and duplicate cases of the active ICSR.

Sender Menu: The sender is usually the secondary source that received the information on the ADR from a primary source. This section contains information about the sender (e.g., pharmaceutical company or regulatory authority), for example the sender's entity, name, contact details and type of sender, as well as the name of the person in the company who is responsible for sending the report.

Reporter Menu: The reporter is the primary source, that is, the person who reported the facts to the DGRM, MAH or to a RPU. This section contains the identification of the reporter, such as its name/initials, contact details, country and professional qualification.

Case data Menu: This menu contains information on the patient who suffered the ADR, such as its name initials, gender, age, date of birth, weight, height, the gestation period of the foetus when it was exposed to the medicinal product (in parent-child cases, when the ADR occurs in the foetus), and evolution of the patient. The **sub-menu clinical history** includes information on other medical conditions that started before the occurrence of the ADR. The **sub-menu pharmacological history** contains the medicines that the patient used before starting the treatment with the suspected medicinal product. The **sub-menu tests** may include the results of any tests performed on the patient. The data included in these sub-menus should be encoded in MedDRA and can additionally be detailed in a text field created to this end.

Patient's Death: This section contains information on the death of the patient, namely the date and cause of death and whether the autopsy was done or not. This section is only filled if the patient has died, regardless of the death being due to a medicinal product or not (natural cause).

Parent Menu: This section contains information on the parent, such as its name's initials, gender, age, date of birth, as well as its clinical and pharmacological history. This section should be filled when dealing with a parent-child/foetus case.

Reaction Menu: At least an ADR reported by the primary source, encoded in MedDRA LLT, along with the reaction outcome (cure, cure with consequences, in recovery, persists without recovery, unknown, death) must be present in this section. Additional important information that should be present in this section is the start and end dates of the reaction, its duration and the temporal relationship between the medicine's administration and the start of the ADR.

Medicinal Product(s) Menu: In this section is inserted the information related to the suspected medicinal products, such as the Proprietary Medicinal Product Name (brand or commercial name) and active substance or DCI (*Denominação Comum Internacional),* the involvement of the medicinal product (suspected, concomitant or interaction), batch, therapeutic indication, route and site of administration, treatment duration, daily dose, temporal relationship between the medicine's administration and the start of the ADR, measure taken relatively to the medicinal product (suspended, increased dose, decreased dose, unchanged dose, unknown or not applicable) and the result of the re-exposition to the product. Furthermore, the company's and reporter's opinion on the relation between the medicinal product and the reaction(s) are also contained in this section.

Narrative/Comments Menu: This section may include any comments from the reporter or the sender, as well as a narrative summarising the case.

2.2.1.3 Reception and Analysis of the Adverse Drug Reaction Reports Sent by the Marketing Authorisation Holders

As already mentioned, the MAHs shall have in place a system for collecting and recording reports of suspected ADRs which are brought to their attention, either reported spontaneously by healthcare professionals or consumers or occurring in a post-authorisation study (59). Besides, the MAHs have the obligation to report to the DGRM, within 15 days of the day on which any person from the MAH responsibility gained knowledge of the event, any serious ADR and other ADRs that qualify for expedited reporting (namely cases of exposure during pregnancy, off-label, medical errors, lack of efficacy and occupational exposure) occurred in Portugal with their

medicinal products that they are aware of. The non-serious ICSRs should be reported by the MAHs to the CAs within the period of 90 days from the date of receipt of the report, only if required by the CA (21, 59). However, during the transitional period (until the EV is completely functional), INFARMED, I.P. does not require MAHs to report the non-serious ADRs.

The send of the serious ADRs between the MAHs and the DGRM is usually done by electronic transmission.

The MAHs that are already in electronic transmission, insert the safety message in their database and it is transmitted via XML directly to the INFARMED's database of ADR, the SVIG.

The MAHs that are not already in electronic transmission have to send their reports by CIOMS form I, which is a reporting form for ADRs internationally recognised. The CIOMS I, as it is possible to see in the Appendix A3, is composed by four parts: part I contains information on the reaction, including data from the patient and the narrative of the case; part II describes the suspected medicinal product(s), including information on the therapy doses, dates and the results of de-challenge and re-challenge; part III contains the information on the concomitant medication as well as other relevant clinical history; and section IV includes information on the manufacturer of the medicinal product (generally organisation that sends the case to the DGRM), the date in which the manufacturer received the information, the date of the report, the source of the report and its type (initial or follow-up). It is desirable that all the fields of the form are completed. However, since in a large number of cases not all the information is available, it must only be ensured that the minimum criteria are present.

The CIOMS I is sent to the DGRM by mail, fax or e-mail. The cases of ADR that arrive by CIOMS I to the DGRM have to be manually inserted in the SVIG by a pharmacovigilance technician. Once inserted in this database, a number is generated – the WWID.

When a case arrives to the DGRM, either by CIOMS I or by SVIG, it is made a validation in order to verify if it contains the minimum criteria (at least one of the following data from the patient: name's initials, gender, age, birth date or age group; type of reporter; at least one suspected/interacting medicinal product; and an adverse drug reaction). If the minimum criteria are not present, it is necessary to request additional information to the MAH, giving them a deadline to send this information. When the solicited information arrives, it is verified again. If the information submitted

is in accordance with the requirements, it must be made a duplicate and a follow-up search and after it, the case is registered as a new case, a follow-up or a duplicate.

2.2.1.3.1 Duplicates Detection and Management

Sometimes, in literature articles, it is only mentioned the active substance of the suspected medicinal product. In these situations, it is probable that the several MAHs of that active substance send an ICSR to the DGRM reporting the same case. This originates duplicate ICSRs. Duplicate cases may also arise when there are two suspected medicinal products of causing an ADR and the MAHs of each suspected medicine send an ICSR to the DGRM or even when a particular ADR is reported to the DGRM by more than one source, for example a MAH and a healthcare professional.

To identify these cases, a duplicate search is made in the SVIG, using information such as the patient name's initials, age, birth date, the adverse reaction(s) and/or the suspected medicinal product(s).

Once the case is open in the SVIG, it should be made a comparison between the possible duplicates relatively to the information in the menus "administrative data", "case data", "reaction", "medicinal product", and "narrative". In duplicate cases from the literature, it is important to compare the data element "literature reference" in the menu "Reporter". When a duplicate of another ICSR is identified, it should be inactivated.

When a duplicate is found, to find out which case should be inactivated and which one should remain active, there are some rules to follow. Therefore, when the same case is sent to the DGRM by two healthcare professionals/consumers or two MAHs, the case that remains active is the one that was sent first, that is, the one that has the oldest date of reception in the sector. The case with a posterior date of reception should be inactivated. When the same case is reported to the DGRM by a healthcare professional/consumer and a MAH, the case that prevails is the one sent by the healthcare professional/consumer and the case sent by the MAH should be inactivated. However, the relevant information present in the inactive case that is not contained in the active case should always be added to the latter.

If the active case belongs to the geographical area of one of the RPUs and the inactive is from a MAH and there is discrepant or additional information, the

collaboration of the concerning RPU can be solicited, in order to clarify any data with the reporter and/or to insert additional information.

2.2.1.3.2 Follow-up Detection and Management

When the MAH has knowledge of new information on a case already sent to the DGRM, this new information should be also sent as a follow-up to the DGRM. Therefore, when a new case arrives to the DGRM and has the same WWID of another case, it is probably a follow-up of a case already in the database.

When a follow-up arrives to the DGRM, it is necessary to verify all the additional information, paying special attention to the dates, since the date of the most recent reception of information must be posterior to the date of initial reception of information by the company and by the sector. Besides that, the data of the new case should be compared with the data of the initial case. If the data of the initial case and the probable follow-up are coincident, the new case is considered a follow-up and the new information is added to the initial case.

2.2.1.3.3 Pharmaceutical Validation and Verification of the Quality of the Individual Case Safety Reports

After the initial validation of an ICSR, a pharmacovigilance technician must analyse all the information inserted in SVIG. This was my main activity during the curricular training at the DGRM. I was responsible for the pharmaceutical analysis and quality verification of the ADR cases sent by the MAHs to the INFARMED, I.P., in the SVIG. This analysis assumes a great relevance, contributing to a more effective signal detection. Next it is presented each section of the ICSR and how it should be analysed in the DGRM. It is important to understand that not all the data elements of each menu need to be filled (since in the majority of the cases not all information is available), but there are some items that must be correctly filled, in order to an ICSR be considered valid and ultimately be electronically transmitted to the European ADR database – EV. Each data element has specificities that are explained in ICH E2B (R2) Guideline.

Administrative information Menu (E2B A.1):

The analysis of any case starts, generally, by the menu of administrative information. In this menu is fundamental to verify the **INFARMED's Number**, **Company Number** and **Safety Report ID**, in order to check if they are correctly constructed.

The INFARMED's Number is a number attributed to all cases by the SVIG. It starts with an X when the case is sent to the INFARMED, I.P. by electronic transmission or with an I when it is sent by CIOMS I and it is manually inserted in the SVIG by a DGRM pharmacovigilance technician responsible for the analysis of the ICSRs exchanged with the MAHs. Following the X or the I, the INFARMED's Number has the year in which it was sent, the month and separated by a hyphen, a random number generated by the database. An example of a possible INFARMED's Number is X201305-0001.

The Company Number or WWID is the identification of the MAH of the product and the Safety Report ID is the identification of the company that submitted the case to the CA. Therefore, the Company Number and Safety Report ID are usually the same. However, they may be different when the company that sends the case is not the holder of the MA of the product, but a hired company to provide pharmacovigilance services to the product's MAH (for example a contract research organisation). When this happens, the Safety Report ID is the one that should be analysed, since it corresponds to the sender of the case.

The Company Number/Safety Report ID is made up of the following elements, separated by a hyphen:

- ISO code of the reporter's country;
- Designation of the entity that creates the case by company's name or identifier code (Company Number)/sender (Safety Report ID) of the case;
- Random number created by the generator entity of the case (Company Number) /sender of the case (Safety Report ID).

The WWID is always the same for a single case and its follow-ups. Therefore, all the versions of a single case have the same WWID. The INFARMED's Number, on the other hand, varies depending on the different versions of a case.

Other data fields present in this menu that are very important to verify are the **reception dates**. In order to the case be considered valid, four data fields in this menu

must be filled: date of initial reception of information by the company, date of initial reception of information in the sector, date of most recent reception of information by the company and date of most recent reception of information in the sector. Therefore, whether it is an initial report, a non-valid ICSR or a follow-up report, there are some aspects to be confirmed.

For an initial report:

- The date of initial reception of information by the company must be the same as the date of the most recent reception of information by the company;
- The date of initial reception of information in the sector must be the same as the date of the most recent reception of information in the sector.

Or, when it is a non-valid ICSR:

- The date of initial reception of information by the company must be previous to the date of the most recent reception of information by the company;
- The date of initial reception of information in the sector must be previous to the date of the most recent reception of information in the sector.

In these non-valid cases, the date of initial reception is the date of receipt of the initial non-valid ICSR and the date of most recent reception is the date of receipt of the new information that allows the case to be considered valid. In these cases, must be referred in the narrative menu that the initial information did not have the minimum criteria.

For a follow-up report:

- The date of initial reception of information by the company must be previous to the date of the most recent reception of information by the company;
- The date of initial reception of information in the sector must be previous to the date of the most recent reception of information in the sector.

For all the reports (initials or follow-up), the pair of dates in the sector and the company should not differ in more than 15 days.

The **Report Type** (E2B A.1.4) is other data element present in this menu. This data element must be correctly filed. Otherwise, it must be requested to the MAH to alter this field. The report can be classified in one of three types: spontaneous, study or other. It is classified as “spontaneous” if it arises from a spontaneous observation or as a “study” if

it is a report from a study (in this case, the data element Type of Study (E2B A.2.3.3) in the reporter menu must be filled). When it is not possible to distinguish from the literature report whether or not the case cited arose from a spontaneous observation or from a study, is should be classified as "other" (69).

The item **Reporter Country** (E2B A.1.1) corresponds to the country that is present in the first part of the WWID. If the reporter of a case is from Portugal, the WWID begins with PT.

The option **Nullified Report** (E2B A.1.13) is selected to indicate that a previously transmitted report should be considered completely void (nullified), i.e, it is not considered a valid ICSR anymore. This can happen for a variety of motives, for example when the whole case was found to be incorrect, when it does not have a single identifiable patient, when the reporter confirms that the patient did not took the suspected medicinal product or took it after the beginning of the reaction. In these cases, since the minimum criteria are no longer met, the case is not an ICSR and therefore it has to be nullified. Only the sender can nullify a case and when it is nullified, it cannot be reactivated. When this item is marked, the data element **Reason for Nullification** (E2B A.1.13.1) must be completed with a brief explanation. This data element is also used when it is found that the case is a duplicate of another individual case previously sent by the same company.

The data element **Medical Confirmation** (E2B A.1.14) should be filled with "yes" when the case is originally reported by a consumer, lawyer or other non-healthcare professional and is confirmed afterwards by a healthcare professional or has medical documentation that confirms the existence of the ADR (for example, the result of a laboratorial test). Therefore, this data element should only be completed when there are two reporters (one healthcare professional and another non-healthcare professional) in the reporter menu. When the case has only a healthcare professional as reporter, the data field E2B A.1.14 should not be filled.

In this menu, it is also very important to verify whether the case is correctly classified according to its seriousness. If it is serious, the option "yes" should be selected in the data element **Seriousness** (E2B A.1.5.1), and chosen one of the options of seriousness criteria: death, life threatening, hospitalisation, temporary or persistent incapacity, congenital anomaly or other medically important condition. When the patient dies and its death is possibly related with the ADR, it must be selected the

seriousness criteria “death”; additionally, the patient death menu must be filled and in the reaction menu, at least one reaction must have the outcome “death”.

Annexes Menu:

This menu contains three sub-menus: annexes, related cases and duplicate cases.

Sub-menu Annexes: In this sub-menu the documents that accompanied the report are attached in XML format, as well as the acknowledgement of receipt files, which are essential in electronic transmission.

Sub-menu Related Cases: This section should be used to identify cases that should be evaluated together, such as a mother-child case where both has reactions, several similar reports from the same reporter, several cases from the same literature article, etc. The related cases should be listed in this section with their identification number (WWID) and the reason why the cases were considered related. The narrative or sender comments’ sections should mention the WWID of the related cases or include a brief description of them.

Sub-menu Duplicate Cases: All the duplicates of an active case must be listed in this section. It is necessary to fill the duplicate number (WWID) and duplicate source of each duplicate case. The duplicate cases of an active case, in turn, should have the WWID of the active case in the authority comments section. The narrative menu of the active case should include the WWID of the duplicate case or include a brief description of it.

Sender Menu:

This section provides information about the sender of the case, who is usually the MAH (although it may be other entity responsible for the electronic transmission). In this section, the fields of Sender’s Entity and Type of Sender should always be completed.

Reporter Menu:

This menu concerns the primary source. In order to be considered a valid case, at least the information on the **Reporter's Professional Qualification** (E2B A.2.1.4) must be present. The possible options available for selection in this field are: physician, pharmacist, dentist, other healthcare professional, lawyer, consumer, or other non-healthcare professional.

When a medical confirmation exists - data element Medical Confirm (E2B A.1.14) in the menu of administrative data filled with "yes" -, it must be added a healthcare professional as primary source (beyond the other primary source).

In literature report cases, only the name of the first author of the article or the investigator should be inserted. In these cases, the data element Literature Reference (E2B A.2.2) must be filled and the format of the bibliographic reference should obey to Vancouver style.

When the option "study" in the section Type of Report (E2B A.1.4), in the administrative data menu, is selected, the data element **Type of Study** (E2B A.2.3.3) in the reporter menu must be filled with the option "other studies" or "individual patient use programs". The field **Study Name** (E2B A.2.3.1) should also be filled.

Case data Menu:

This menu contains four sub-menus: patient data, clinical history, pharmacological history and tests.

Sub-menu patient data: In order to be considered a valid case, at least one of the following data elements must be filled:

- The initials of the patient's name. This data element should not be filled with other abbreviations/words that do not identify the patient, such as UNK or Unknown. Therefore, when the patient's initials are unknown, this data element should be empty;
- The gender of the patient;
- The birth date, age or age group of the patient.

When none of these data elements are filled, it has to be made a request to the MAH. If the MAH cannot give this information, the case has to be nullified, because it does not present the minimum criteria.

In a parent-child case and when the ADR occurs in the foetus, the data element **period of gestation** (E2B B.1.2.2.1a) should be filled, when the foetus was exposed to the medicinal product in the uterus. In such cases, the information in this sub-menu only concerns the foetus and the information on the parent should merely be included in the parent menu. When a reaction occurs in the parent and in the child/foetus, two reports are applicable (these two reports should refer each other's WWID through the menu related cases). In cases of early spontaneous abortion, only a parent report should be created.

Other data elements present in this section that may be filled in order to allow a better analysis of the case are the patient height, weight, last menstrual period date and evolution.

Sub-menu clinical history: When there is information regarding the clinical history of the patient in the narrative, such information should be included in this menu. This information must be encoded in MedDRA terminology and can additionally be detailed in a text field created to this end. This menu includes the relevant medical history of the patient and concurrent conditions (not including the ADR), for example diseases relevant to the case, conditions, surgical procedures, etc. Imprecise dates can be used for the start and end dates of the conditions (69).

Sub-menu pharmacological history: Any information about pharmacological history present in the narrative should be listed in this menu. It is considered pharmacological history the medicinal products that were discontinued before the start of the treatment with the suspected medicinal product and/or that at the time of the reaction it is unlikely that the products were still in the body. Therefore, the concomitant medication or the medicinal products used for the treatment of the reaction are not included in this menu. Inaccurate dates can be used for both the start and end dates of the medicinal products.

Sub-menu tests: If there is any information on the results of any tests performed on the patient in the narrative, such information should be provided according to the MedDRA

terminology in this menu, and can additionally be detailed in a text field created to this end.

Patient's Death Menu:

This section is only filled if the patient has died, regardless of the death being due to a medicinal product or not (natural cause). These two situations must be analysed and processed in a different way. Therefore, if the patient's death is supposedly related to the ADR, the seriousness criteria (E2B A.1.5.2) of the case must be filled with "death"; additionally, at least one of the adverse reactions must have the outcome (E2B B.2.I.8) "death". If the patient's death is considered not related to the ADR, only the patient's death menu should be filled, that is, the seriousness criteria of the case must not be filled with "death" and no ADR may have the outcome "death". In both cases (death due to ADR or not), the fields corresponding to the **date and cause of death** in the patient's death menu should be filled according to MedDRA terminology, if that information is known. Similarly, if there is information on the autopsy report, it can be mentioned in this menu.

Parent Menu:

This section is only used for a parent-child/foetus report and where the parent had no adverse reaction. In these cases, at least one of the following fields must be filled: parent age, parent birth date or parent sex.

Reaction Menu:

This menu should contain at least one **adverse reaction** encoded in MedDRA LLT, since it is a minimum criteria. As already stated in this report, the chosen term should be the MedDRA LLT more closely corresponding to the reaction as reported by the primary source. The document MedDRA Term Selection: Points to Consider should be consulted by the sender during the adverse reaction codification and by the pharmacovigilance technician during the analysis of the ICSR.

The data element **outcome of the ADR** must be filled for every ADR and according to the narrative text, so that the case can be validated. As already mentioned, when the patient's death is possibly related to the reaction, the outcome "death" should

be selected. In these cases, the seriousness criteria of the case must be equally "death". In the cases where the death is unrelated to the reaction, according to both the reporter and the sender, the outcome "death" should not be selected in this field, but should be reported only in the menu patient's death.

When the outcome of the ADR is "unknown", "recovering" or "persists without recovering", it is fundamental the tracking of the case and the request of a follow-up to the MAH.

Other important data elements in this menu are the **start and end dates of the reaction**, especially the start date, in order to confirm that the ADR occurred only after the intake of the suspected medicinal product. The field corresponding to the **duration of the reaction** should also be verified and can usually be computed from start/end of reaction. Both dates and duration of the ADR may be useful for the evaluation of the case (69).

The data element correspondent to the **interval between the administration of the suspected medicinal product and start of the reaction** is especially important in some circumstances, such as when only imprecise dates are known but there is more information about the interval. When there is more than one suspected medicinal product, more than one ICSR can be used in order to provide all the intervals between the reaction and all suspected medicinal products. In these situations, it should be indicated that the reports are linked in the sub-menu related cases (69).

Narrative:

The narrative text should be presented in a sequential manner, preferably by chronological order and should contain a summary of the case with the minimum criteria and relevant data, information related to the clinical evolution of the patient, administrated medicinal products, procedures conducted and the patient outcome.

In follow-up cases, the text of the previous version of the narrative should be maintained and the additional information should be included at the end of the narrative, preceded by the date in which that information was obtained by the company, with reference to "follow-up".

Medicinal Product(s) Menu:

In this menu, all the suspected and concomitant medicinal products referred on the narrative section are listed, according to their involvement in the reaction (suspected, concomitant or interacting). The medicinal products referred on the narrative that are considered pharmacological history, as well as the ones used for the treatment of the ADR(s), should not be inserted in this menu. In order to be a valid case, this menu must include at least one medicinal product with the involvement "suspected" or "interaction". The medicinal products can be codified by Proprietary Medicinal Product Name, active substance or DCI. However, it is desirable that the medicinal products are coded with the brand name, when this information is known. The biological products should always be identified by brand name and batch number. A medicinal product should not be coded by therapeutic class. This information may only be included in the narrative section.

It is very important that the field concerning the **measure taken relatively to the medicinal product** is correctly fulfilled with one of the following options: suspended, increased dose, decreased dose, unchanged dose, unknown or not applicable. It is also important to know the result of **rechallenge**. This field should only be completed if it is known that a rechallenge was done. The word unknown in this field means that a rechallenge was done but it is not known whether the reaction recurred or not (69).

The reporter may add other type information related to the medicinal products in this menu, which facilitates the analysis of the case. When in the narrative section is mentioned, for the medicinal product(s), its(their) therapeutic indication, start and end dates, duration of therapeutic, route and site of administration, daily dose, etc, such information should be structured in the respective E2B fields of this menu.

The MAH's and/or reporter's opinion on the likelihood of the adverse reaction being caused by the suspected medicinal product(s) is also structured in this section.

2.2.2 Risk Minimisation

2.2.2.1 Risk Communication

The risk communication is a part of the risk minimisation activities. The risk minimisation activities are developed to allow a safer and effective use of a medicinal

product throughout its life cycle and may consist of routine or additional activities. The routine risk minimisation activities are a set of activities that apply to all the medicinal products and include measures associated with locally authorised product labelling, such as the PIL and the SmPC, the pack size(s) or the legal status of the product (47). The additional risk minimisation activities are those measures which are not included in the routine activities and should only be suggested when there is a safety concern that cannot be managed through the routine risk minimisation activities. Examples of additional risk minimisation activities are the Direct Healthcare Professional Communications (DHPCs) and educational materials distributed to patients and/or healthcare professionals.

All risk minimisation activities should have a clearly identifiable objective and should be reviewed regularly in order to evaluate their effectiveness (47). The SRs are a way to monitor whether the risk minimisation activities for a specific product are being effective or not. For example, if there is a medicinal product with a known teratogenic potential for which there are risk minimisation activities implemented to prevent pregnancies, such as educational materials for patients and healthcare professionals, and a case of pregnancy in a patient taking this product is reported, it means that the programme of risk minimisation may have failed and there is a need to review and change this programme.

During my training at the DGRM, I had the chance to observe the evaluation of educational materials and to validate DHPCs.

2.2.2.1.1 Educational Materials

The educational materials are part of the additional risk minimisation activities. The distribution of educational materials to healthcare professionals involved in the prescription, dispense or administration of a medicinal product and/or the consumers is a minimisation risk measure that may be necessary to implement when important or potential risks with a medicinal product are identified or when there is a lack of safety information.

The educational materials, generally, are specified at the time of MA grant, accompany the medicinal product throughout its life cycle and are distributed along with it. The need for the development of educational materials depends on a specific safety concern with a medicinal product and has the following objectives:

- To increase the awareness about specific risks of the medicinal products;
- To allow the early detection and prevention of ADRs;
- To enhance the understanding on the measures used to reduce the frequency and seriousness of the ADRs;
- To provide information to the healthcare professionals and patients.

The type of the educational material depends on the objective and the audience to whom it is targeted. Examples of educational materials are prescription guides for physicians, dispensing guides for pharmacists, checklists for healthcare professionals and patients, patient information brochures/booklets, patient alerts and reminder cards or specific training programmes. The educational materials should be available in a range of different formats (paper, audio, video, web, in-person training), in order to ensure that the access is not limited by disability or access to the internet. For example, when the target of the material is the patients with eye sight problems, the audio format may be the most appropriate.

All the educational materials of medicinal products to be implemented in Portugal must be previously approved by the INFARMED, I.P.. Therefore, the MAHs develop the educational materials and submit them to the DGRM in order to be evaluated by a pharmacovigilance technician. The evaluation is intended to verify if the educational material contemplate the information that is required, if it is aligned with the currently approved product information for a medicinal product, such as the SmPC and PIL, the proposed recipients to whom it will be distributed, the format of the material, the date of the distribution as well as other graphical aspects. The educational materials cannot include any promotional element and must be restricted to the risk(s) related to the product and the management of those risk(s), providing clear, concise and objective messages. Therefore, the educational material should be clearly distinct and distributed separately from any promotional material the MAH produces. This is another important aspect to analyse in the process of reviewing the materials by the DGRM. After the validation of the material, it is sent to the MAH with all the amendments and comments. If the MAH allows, it is later published in the website of the INFARMED, I.P..

Although I did not have the opportunity to validate educational materials during my traineeship at the DGRM, I was taught how this validation is done and the aspects worth considering during this process.

2.2.2.1.2 Direct Healthcare Professional Communication

A DHPC is a communication intervention sent by a MAH or a CA that delivers important safety information in relation to a medicinal product directly to the healthcare professionals, informing them of the need to take certain actions or adapt their practices (76).

A DHPC may convey several types of information relevant to the patients' safety. Examples of that are information on the suspension, withdrawal or revocation of a MA for safety reasons, a restriction in availability or discontinuation of a medicinal product, new major warnings or precautions for use in the product information, important changes to the SmPC of a medicinal product for safety reasons, such as a new contraindication, a restriction in the therapeutic indications or a change in the recommended dose, etc (76). The letters must provide recommendations to the healthcare professionals on how to minimise a specific risk and should start with an explanation of the reason why it is being distributed. These letters generally contain information that should be primarily of the prescribers' knowledge (if possible), because it allows a better communication of the risks to the patients.

The preparation of DHPCs for medicinal products intended for distribution in Portugal involves the cooperation between the MAH and the DGRM. The content of this communication is proposed by the MAH of the medicinal product and its final version is agreed with the DGRM (even if its content has already been agreed between the MAH and EMA or another MS) before it can be issued to the healthcare professionals by the MAH. This agreement covers not only the content of the information and translation, but also the communication plan, including the intended recipients and the timetable for disseminating the letter. Therefore, when there is a need to transmit safety information on a medicinal product to healthcare professionals, the MAH have to submit the DHPC to the DGRM for validation. During my curricular training at the DRGM I had the opportunity to validate two DHPCs concerning updates to the SmPC of two medicinal products. This validation included the verification of the content of the information in the letter (to see if it is consistent with the SmPC, for example), the translation, the information about the MAH and the INFARMED, I.P., the list of the target groups to whom it will be distributed (depending on the subject and the medicinal product in question, the DHPC can be distributed between specific groups of healthcare professionals, patient groups, pharmacies, wholesalers, etc), the distribution

method (e-mail, mail, visit, etc) and the agreed communication plan, or the expected date for the distribution of the letter. Besides this, it is also verified if all the requirements are fulfilled, such as the format of the letter. It is advised that the MAHs follow the template for DHPCs present in the Annex II of the GVP. It is important to have in mind that the letter should be objective and concise and should be presented in a simple language.

The proposed changes made to the letter by a DGRM pharmacovigilance technician are sent to the MAH. Later, the MAH replies saying whether or not they agree with the proposed changes and answering any question that has been asked. After this e-mail exchange, which may be brief or long (always paying attention to the dates for the sending of the DHPC) and when everything is agreed and clarified between the MAH and the DGRM, the MAH sends the letter to the agreed recipients and, ultimately, the MAH is asked if they authorise the publication of the DHPC in the website of the INFARMED, I.P..

2.2.2.2 Type II Safety Variations

A variation to the terms of a MA means an amendment to the contents of it. The variations to medicinal products can be classified in different categories, depending on the level of risk to the public and the impact on the quality, safety and efficacy of the medicinal product concerned. Therefore, there are four types of variations: minor variations of type IA, minor variations of type IB, major variations of type II and extensions (77).

The type of variations analysed at the DGRM are those that concerns major changes in the safety profile of a medicinal product. These major safety variations are a type II variation. The Commission Regulation (EC) No 1234/2008 defines a variation of Type II as a variation that is not an extension and may have a significant impact on the quality, safety or efficacy of the medicinal product concerned (77).

The safety type II variations requested by the DGRM are safety measures intended to modify the information contained in the SmPC and the PIL of the medicinal products for which it was identified a potential safety concern (78). In order to do this, the DGRM notifies the MAHs of those medicinal products to submit the respective application for a type II safety variation. The DGRM establishes a deadline for the

submission of the necessary documents by the MAH, which will depend on the urgency and potential impact on the public health of the safety concern.

After receiving the application for the safety variation from the MAH, the pharmacovigilance technicians of the DGRM validate and review the documentation received and send it to the MAH to get their approval on the proposed changes. When an agreement is reached, the type II safety variation must be approved by the Director of the DGRM and, finally, by the INFARMED's Executive Board.

Unfortunately I did not have not the opportunity to conduct safety variations, but it was explained to me how this process is performed at the DGRM.

2.2.2.3 Rapid Alert and Non-Urgent Information System

In the EU, there is a pharmacovigilance alert system between the CAs of the MSs, the EMA and the EC that allows the exchange of safety concerns, such as those that may result in major changes to the MA status or revocation/withdrawal of a product, with the appropriate degree of urgency. Therefore, there are two types of communication systems, which may be initiated by one of the CAs of the MSs or by the EMA: the Rapid Alert (RA) and the Non-urgent Information System (NUI) (79).

The RAs are used to communicate at an early stage (usually before a decision is taken in a MS) any safety information that potentially has a major impact on the known risk-benefit balance of a medicinal product and that may require a prompt regulatory action and a communication to healthcare professionals/general public in order to protect the public health. This information must be shared within 24h between the CAs, the EMA and the EC, so that it can be decided the appropriate action to be taken to minimise the risks derived from the safety concern. Examples of the type of information that may be conveyed by a RA are an urgent safety restriction, suspension, revocation or withdrawal of a MA, and/or recall of the product from the market, suspension of marketing and/or use of a medicinal product, important changes in the SmPC (such as new contraindications), a need to inform healthcare professionals or patients about an identified risk of a medicinal product as soon as possible, among others (79).

The initiator of a RA requesting information is responsible for gathering the several responses to the RA and circulate it to all the MSs, EMA and EC no later than one week after the receipt of the RA (79).

A NUI should be used for collection and exchange of pharmacovigilance information that does not fulfil the criteria for a RA, that is, less urgent information, between the CAs and the EMA. Therefore, a NUI should be used to transmit safety concerns that do not require immediate or urgent action and/or where additional information to support the evaluation of the concern is required from other MSs (79).

The initiator of a NUI establishes a time frame for the other MSs to send their responses. The initiator, after the receipt of the NUI responses, develops a document compiling all the responses and circulates it to all MSs, EMA and EC (79).

The compilation of the responses to a RA or NUI should include, at least, the original RA/NUI and all the responses from the MSs (79). Following a RA or NUI, the safety concern is ultimately reviewed and discussed in the PRAC, in order to evaluate the need of any regulatory action.

Most of the RAs and NUIs processed at the DGRM are sent by other CAs or by the EMA. In these cases, the DGRM pharmacovigilance technicians (from the team responsible for the risk minimisation activities) analyse the documentation, search and collect the required information and elaborate the response. This response, as well as any other needed data, is insert it in the European Pharmacovigilance Issues Tracking Tool[7] (EPITT) and sent to the address list "All Human Regulatory Authorities", which refers to the contact points of the CAs of the MSs, the EMA and the EC.

When these processes are started by the DGRM, the pharmacovigilance technicians are responsible for developing a document explaining the safety concern, which is inserted in the EPITT and sent to the address list "All Human Regulatory Authorities". In these situations, the DGRM pharmacovigilance technicians are also responsible for the reception and compilation of all the RA/NUI responses into a document and include it into the EPPIT, in order to circulate between all the others MSs, EMA and EC.

As with the safety variations, I did not participate in the processing of RAs and NUIs. However, I had the chance to see how these processes were conducted.

[7] The EPITT is a web-based system developed by the EMA that tracks and monitors the safety of the medicinal products, including the monitoring of safety signals and safety issues discussed in the PRAC, the tracking of NUIs and RAs, PSUR cycles' and timetables' assessments conducted by the CAs and Risk Management activities.

3 Complementary Learning

3.1 Publications

3.1.1 Updates to the Southern Regional Pharmacovigilance Unit Website

Taking into account the importance of the online reporting of suspected ADRs, it seems to be crucial that the UFS has a website with clear information and with easily accessible content. Therefore, I was asked to give suggestions in order to improve the UFS's website. Besides the several suggestions I gave, I was responsible for the elaboration of some sections of the website, namely: the presentation of the UFS, its mission, functions and constitution, the description of the NPS, what pharmacovigilance representatives are (including their contacts), as well as several useful links.

However, the format and content of the website was not yet updated, since the person responsible for the informatics at the FFUL was not available.

Additionally, I was also required to make an explanatory note, to be on the website, on how should be done the reporting of quality problems with a medicinal product and non-conformities of medical devices. This note is currently on the initial page of the UFS's website.

3.1.2 Elaboration of an article

During my time at the UFS, it was suggested to me to elaborate an article on the role of pharmacovigilance representatives in the NPS, to be submitted to a scientific journal. This article is currently being finalised and reviewed.

The figure of pharmacovigilance representative was mentioned for the first time in the Ordinance No 605/99 and is defined in the Decree-Law No 128/2013 (21, 24). The UFS initiated the use of this figure in 2008, being the first RPU in Portugal, and the only one at this moment, to integrate pharmacovigilance representatives in its structure.

3.1.3 Adverse Drug Reactions' Guide

The Adverse Drug Reactions' Guide is a manual written by the UFS and Northern RPU that describes several ADRs by organic system. Each chapter of this guide is

related to a specific organ system. The UFS is developing the chapter of gastrointestinal ADRs. During my trainee, I had the opportunity to participate in the elaboration of this chapter, elaborating two fascicles on the following subjects: xerostomia and taste disorders - hypogeusia, ageusia and dysgeusia.

This guide is available for the public and may be consulted in the web-portals of the UFS and Northern RPU. The volume on gastrointestinal ADRs will be published as soon as it is concluded.

3.2 Oral Presentations

During my training I was asked to make several oral presentations.

On the first day of training, I was asked to prepare a presentation about the New European Pharmacovigilance Legislation and to present it to the internal staff of the UFS within a month. After this presentation, I had to deliver three more presentations on the same subject, although with slight changes in the content, taking into account the different audience. These presentations took place:

- At a meeting of the iMed.UL group, a research centre located at the FFUL, for university teachers and doctorate students, on 26 November 2012;
- At a meeting between the UFS and the pharmacovigilance representatives, on 7 December 2012;
- At the "XV Course of Practical Pharmacy", for all the 5th year students of Pharmaceutical Sciences of the FFUL, on 2 February 2013 (Appendix A4 and A5).

Besides these presentations, I participated in six workshops of Pharmacovigilance, with case studies on the processing of SRs in the UFS, also for all the 5th year students of Pharmaceutical Sciences of the FFUL.

All these presentations were, without any doubt, really challenging for me, since I had to overcome one of my biggest fears which was talking in public.

3.3 Trainings, Courses and Workshops

During my trainee as a pharmacovigilance technician, I had the opportunity to attend several trainings, courses and workshops. In this section, I will provide a brief description of all these courses.

During the months of October, November and December 2012, it was given me the opportunity to frequented the classes of **Pharmacovigilance** of the **Master degree in Regulation and Evaluation of Medicines and Health Products (RAMPS)**, carried out in the FFUL. This course, integrated into Master RAMPS, had the duration of thirty hours.

In these classes were addressed several topics related to the safety monitoring of medicines, varying from regulatory to clinical aspects. Specifically, the classes addressed the following topics:

- The NPS in Portugal and in Europe;
- The new pharmacovigilance legislation;
- The SRs;
- The process of causality assessment;
- The mechanisms of ADR at the level of several systems and organs, namely cutaneous, hematologic, gastrointestinal, hepatic, renal, neurologic and cardiac ADRs.

My participation in this course allowed me to consolidate some of the knowledge already acquired in the area of pharmacovigilance (at the regulatory level, but also at the level of the pathophysiological aspects of some ADRs), as well as to obtain new knowledge relevant for my professional life.

On the 25th/26th January and the 8th/9th February 2013, I had the opportunity to attend the lectures of the module "**Pharmacovigilance and Risk Management**", included in a Post-Graduate Course, which occurred in the FFUL. This course, with the aim to promote the acquisition/improvement of the knowledge in the field medicines safety, pharmacovigilance and risk management, addressed the following topics: the concept of iatrogenesis, clinical and epidemiologic aspects of ADRs, pharmacogenomics, risk management systems and plans, observational studies to assess the safety of medicinal products, namely PASS and prescription-event monitoring.

On December 7th, 2013, I attended an oral presentation by a doctorate student about an "**Intensive monitoring in Portugal – A model to access medicines in real life conditions**" that is being conducted in the Centre for Health Evaluation & Research (CEFAR), a contract research organisation of the Portuguese National Association of Pharmacies Group. I personally considered this presentation very interesting, since it highlighted the relevance and the need for more active safety monitoring of the marketed medicinal products, which take into account some of the limitations of spontaneous reporting.

On the February 27th, 2013, I attended a workshop of the iMed.UL postgraduate Students Commission about "**Tools for managing bibliographic references**", organised by the CEFAR (Appendix A6). In this workshop I was able to learn more about the different types of tools that can be used for managing references, their advantages and disadvantages.

On the February 28th, and the March 1st, 2013, I attended the "**EU regulatory workshop on medication errors**". This two-day workshop was organised and took place at the EMA and I was able to follow it live through a stream at the facilities of the INFARMED, I.P.. This workshop had the objective of bringing to attention that the medication errors constitute an important public-health issue and to discuss the new legal requirements for reporting and processing medication errors. This workshop helped me to understand the magnitude of the problem of medication errors and how important it is to report these situations. Besides, I learned that several European countries have two different systems to process medication errors, depending on whether the medication errors result in harm for the patient or not. It was emphasised, as it is stated in the Module VI of the GVP, that the information on medication errors with no associated adverse reaction should not be reported as an ICSR, but they should be considered in PSURs. Therefore, it is important to gather this information. Since there is no other organisation in Portugal that is able to collect the information on medication errors with no associated adverse reaction, this is collected by the NPS, in order to be sent later for the MAHs. However, this information should not be transmitted to the EMA. This matter was further discussed in a meeting between the DGRM and RPUs collaborators.

On the April 17th, 2013, I attended another workshop of the iMed.UL postgraduate Students Commission named "***Curriculum Vitae* (CV) and motivation letters**"

(Appendix A7). In this workshop I learned the best way to organise a CV, what should be said and what should not be said in a CV, how to write a motivation letter and how to correctly write an e-mail. Taking into consideration the phase of my life in which I find myself in, I think it was very helpful to attend this workshop.

On the May 7th, 2013, I attended the ***Manhãs informativas*** of the INFARMED, I.P. on the **New Pharmacovigilance Legislation**, more specifically, the impact of it in the pharmacovigilance activities (ADR reporting, additional monitoring, signal detection, RMP, PSUR, PASS, etc), the articulation with the PRAC, as well as the impact in the regulatory activities (MAs, variations, renewals, and referrals). Most of the concepts presented in this session were already familiar to me, since I had to study in depth the new legislation for the presentations I gave on this subject. However, once the legislation is still being implemented, there are news and updates in this area almost every day. So, it is important to attend these sessions, which present the most up-to-date information.

On the May 15th, 2013, I attended a conference at the INFARMED, I.P., with the name **"Biosimilar medicinal products"**. Although the theme of this conference is not directly related to my training in the area of pharmacovigilance, I decided to attend it because I wanted to know more about biosimilars, given the great importance these will have in the next decades. This conference focused on the scientific, legislative and economic side of biosimilar medicinal products, at a national and European level, namely the access of the biosimilars to the EU markets, impact of biosimilars in the public expense and the experience of using biosimilars in Portugal.

During my curricular training in the DGRM, I had the opportunity to attend the **I Post-Graduated Course in Good Clinical Practices**, of the Centre of Clinical Investigation at the academic centre of medicine of Lisbon (Appendix A8). This course took place on the May 22nd and 23rd, 2013, at the Faculty of Medicine of the University of Lisbon and had the duration of thirteen hours. Although the subjects addressed in this course were not new to me, since I had already learned it during my Master's Degree, it reminded me of some concepts that were forgotten. Therefore, and although the subject of the course is not directly related to my curricular training in the area of pharmacovigilance, I enjoyed participating in this course and I really appreciated having this opportunity.

3.4 Meetings

The UFS organised a meeting with the pharmacovigilance representatives on December 7th, 2012, in the FFUL. I was responsible to prepare the agenda and the minute of the meeting. Additionally, and as already mentioned, I delivered an oral presentation about the new European Pharmacovigilance Legislation in this meeting, emphasising the changes on the definition of ADR, the definition of overdose, abuse, misuse, off-label use, occupational exposure, and what constitutes an ICSR and what do not, so that the representatives know what they should report.

At this meeting, there was also a presentation by a pharmacovigilance technician from the DGRM on the new online platform for ADR reporting – the PortalRAM –, instructions on how to use it and its potentialities, as well as a discussion about the little usage of this tool for the spontaneous reporting of ADRs.

Besides, there was a discussion on potential studies of intensive monitoring on hospital/community pharmacy conducted by the UFS in collaboration with the pharmacovigilance representatives.

The UFS participates in the meetings of the iMed.UL group, a research centre located at the FFUL, composed by university teachers and doctorate students. The participation of the UFS in these meetings is important since it may collaborate in some of this centre's studies. During my 6-month training at the UFS, I had the opportunity to participate in three meetings of this group. In one of these meetings, as already stated, I made a presentation about the new European Pharmacovigilance Legislation. In the other two meetings, I attended to other presentations on relevant subjects, namely about the Delphi Method, which is a process used to reach consensus that I was unaware of until then, and about the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) group, a collaborative network coordinated by the EMA and developed in collaboration with pharmacoepidemiology and Pharmacovigilance European experts, which facilitates the conduction of post-authorisation studies focusing on safety and on the benefit-risk balance.

On March 12th, 2013, the DGRM summoned all the RPUs for a meeting at the INFARMED, I.P. facilities, with the aim to implement a Quality Management System in every RPU, as a requirement of the Commission Implementing Regulation (EU) No 520/2012 of 18th of June 2012. Therefore, it was discussed what a Quality Management

System is, the way the RPUs should implement it and the date limit for its implementation.

In this meeting there was also a presentation and a discussion about the SRs received by the NPS in the year of 2012, comparing the results between the four RPUs.

It was also given an explanation on how to process ADR reports associated with suspected quality problems of a medicinal product and on special cases of SRs, for example the situations of off-label or medication error with no associated adverse reaction, or cases of exposure to a medicinal product during pregnancy, with no abnormal outcome for the embryo or foetus following this exposure. Since these situations do not constitute an ICSR, they must be processed in a special manner and it was given a work instruction to do so.

This explanation was, unquestionably, very useful, because it allowed me to clarify what should be done when it is received a SR with no associated adverse reaction, helping me interpreting the GVP module VI, which is not clear enough in this matter.

Overall, I considered this meeting very important, since it contributed for the standardisation of practices and share of opinions and ideas between the several RPUs and the DGRM.

4 Discussion

4.1 Tasks Assigned and Learning Outcomes

During my curricular training I had the opportunity to develop activities as a pharmacovigilance technician in two different institutions: the Southern Regional Pharmacovigilance Unit and the National Authority of Medicines and Health Products. It gave me the chance to work with different teams, to know different people and to understand how two different organisations work.

My curricular training was most of the time focused on the activities of processing SRs from the healthcare professionals and analysis of ICSRs sent by the MAHs. I only had a brief contact with risk minimisation activities. It provided me with an opportunity to solidly increase my knowledge and interest in the pharmacovigilance area.

The contact with real work environment definitely enabled me to develop and improve my ability to work, my hard skills, which were already described along this report, and my soft skills (both intrapersonal and interpersonal skills).

The knowledge acquired during my academic journey was complemented and became clear. Besides, I had the chance to closely analyse the articulation of the NPS and the interactions between a CA, the healthcare professionals/consumers, the MAHs and the international bodies.

One important soft skill improved was the autonomy. During my training, I was confronted with new situations that I surpassed by reading and interpreting the current legislation. On the other hand, my teamwork was also greatly improved, since I had to work in teams with my colleagues of the UFS and DGRM several times.

My verbal and non-verbal communication skills, as well as my self-confidence, were also greatly improved. This improvement allowed me to discuss my ideas assertively and to communicate in a more easy and effective way.

I had also to develop organisational skills and to learn how to manage my time, planning and defining priorities when there were several tasks that had to be done in a certain period of time, in order to ensure that the activities were finished in an efficient way, according to the procedures and deadlines.

Another important skill that I developed was the responsibility sense. I learned to pay attention to all the details in order to minimise potential errors, since the

pharmacovigilance activities conducted at the UFS and DGRM are very important and may have a high impact at a national and international level.

After these 9 months of professional experience, I believe I have successfully accomplished all the objectives proposed in the introduction of this report. It was possible mainly due to my academic journey at the University of Aveiro, which definitely provided me a great background to conduct the described activities. In fact, during all my academic formation I was encouraged to be autonomous and to work in teams. The development of these skills started in the beginning of my Degree in Biomedical Sciences, through the teaching methodology used – the Problem-Based Learning. In this model, in order to learn a subject, students are given every week challenging and realistic problems that has to be solved by studying at home and then discussed in group toward their resolution, allowing the development of a strong critical spirit, effective problem solving and collaboration skills, autonomous learning and intrinsic motivation. The Problem-Based Learning also provides students a better preparation for the resolution of real life problems, a great familiarity with several sources of information and ease in the search of information. Therefore, there is no doubt that this teaching method prepared me in the best way to face new situations and looking for solutions to the problems found.

Besides all these soft skills, I cannot fail to mention all the hard skills acquired during my Degree and Master, from knowledge in anatomy and pathophysiology to pharmacovigilance and other regulatory aspects present throughout the entire life cycle of the medicinal products.

Although I achieved the proposed objectives, there were some activities that I would have liked to have done, but unfortunately I did not have this opportunity since my training at the DGRM only had the duration of three months. I would have liked to participate in more activities of risk minimisation in the DGRM, such as the processing of type II safety variations, RAs and NUIs and the evaluation of PSURs and RMPs. Also, I would have liked to have the opportunity to participate in the evaluation of educational materials and to validate more DHPCs.

Nonetheless, I believe I took the best of the opportunities I was given. I appreciated the constant support given by my colleagues both at the UFS and the DGRM and I am really glad for all the knowledge and lessons that this training brought me.

4.2 Difficulties Felt During the Curricular Training

The transition from my academic to professional life was a challenge to me, since I had to adapt to a new context, new people and other responsibilities. The fact of having come across very good work environments, and both the collaborators of the UFS and the DGRM being nice and kind, always ready to give me all the necessary support, made this process easier.

Next, I am going to detail some challenges and difficulties felt during my curricular training, both at the level of my soft skills and at a more technical level, with difficulties felt in specific procedures of my work.

Difficulties felt at the level of my soft skills

The new pharmacovigilance legislation, as already mentioned, brought new requirements and challenges for all the partners of the NPS. My curricular training occurred during the phase of implementation of this legislation and, therefore, in a phase of huge changes, when there are several processes that are not fully explicit and everyone wants to be informed but sometimes it is not easy to find the information needed, since not all the GVP modules are finished yet. Moreover, the interpretation of the information contained in the guidelines is not always easy. Therefore, I felt the need to be constantly updated and to read the available guidelines in order to understand certain procedures and to know how to answer the questions that I was asked. This autonomous study gave me the opportunity to learn more about the foundations of the new legislation and the pharmacovigilance procedures. Part of this autonomy was developed during my academic journey, where since the beginning we were stimulated to be autonomous and to be prepared for facing new situations. In fact, during my training I had to face new and challenging situations that I overcame by searching for solutions and discussing my ideas with my colleagues. Furthermore, in a transition period it is normal that not everything works 100% and there are always things that do not go as planned. For example, during my training at the UFS, the PortalRAM would constantly show error messages, delaying the work a lot. It was, hence, a complicated phase, but also more challenging to me.

Furthermore, my communication skills were definitely a problem to me, since I have an introverted personality. All the oral presentations I had to make during my training were, without a doubt, really challenging for me, since I had to overcome one of my biggest fears which is talking in public. In fact, the lecture I made for the Course of Practical Pharmacy had an audience of over one hundred people, and I had never spoken to such a large number of people before. I believe that these oral presentations as well as the curricular training on itself greatly contributed to enhance my communication skills and to prepare me to my professional life. However, I know that I have yet to evolve and improve this aspect.

Another challenge I came across during my training were the phone calls for follow-up to the reporters of the SRs, since during the first phone calls I felt nervous, but with time, those phone calls became easier for me. In the beginning of my training in the UFS, the follow-ups with the reporters were made by the other collaborators of the UFS. However, with time, I gained autonomy at this level and started contacting directly with the reporters, being responsible for all the processing of the SRs from start to finish. I learnt that, to gain confidence for these phone calls, it is fundamental to prepare in advance the questions that I am going to ask to the reporter, to analyse in depth the case and to do the necessary search in order to demonstrate a full knowledge of the situation and to be able to respond to any questions made by the reporter.

Difficulties felt during the processing of SRs and analysis of ICSRs

As already mentioned in this report, the MedDRA codification of the ADRs is not always easy. Next, I am going to exemplify a situation where I had some difficulties attributing the correct MedDRA code for one of the ADRs reported. A healthcare professional reported a case in which a patient presented indisposition (*má disposição),* surfeit *(sensação de enfartamento*) and loss of appetite (*perda de apetite*) after using a certain medicinal product. The term indisposition may assume different meanings and, consequently, different encodings: a general feeling of being unwell, which could be encoded in the LLT "malaise" that belongs to the SOC "General disorders and administration site conditions", or an indisposition like nausea, which in this case would be encoded with the LLT "nausea" that belongs to the SOC "Gastrointestinal disorders". As the reporter was not available to be contacted, and after discussing the case with the

collaborators of the UFS, I assumed that this indisposition would probably be related the gastrointestinal system, since the remaining ADRs reported suggested a problem at the level of this system and, consequently, with the feeling of nausea. Therefore, I coded this ADR with the LLT "nausea".

Another difficulty felt in the processing of SRs was in the classification of the ADRs as expected or unexpected. This process is not linear and there are some situations where the terms found in the SmPC are not exactly the same as the ones described by the reporter, but they are, in a certain way, related. For example, considering the case previously described, in which the patient presented indisposition (*má disposição),* surfeit *(sensação de enfartamento*) and loss of appetite (*perda de apetite*) after using a certain medicinal product: the term surfeit was not present in the SmPC of that medicinal product, but instead similar conditions such as dyspepsia or indigestion. In this case I had doubts about whether to consider the ADR expected or unexpected for that product. After discussing the situation with the other collaborators of the UFS, we considered that the surfeit felt by the patient was essentially the same as an indigestion, so we considered this ADR expected.

Also, the process of causality assessment is complex and can be, sometimes, quite subjective. In fact, sometimes it is not easy to decide between two causality categories, for example between the certain and the probable or the probable and the possible. The process of attributing an event to a medicinal product requires some clinical knowledge. In this aspect, the knowledge acquired during my degree in the scope of anatomy and physiology was extremely useful.

It is desirable to have a meeting between the UFS collaborators and the clinical expert within every 15 days in order to conclude the cases that await the causality assessment and to meet the deadlines. However, most of the times, it was difficult to communicate with the clinical expert due to many rejected phone calls and postponed meetings. Since the clinical expert has limited time available for these meetings, when it is possible to schedule a meeting, it is fundamental to have the cases ready and reviewed and, during the meeting, it is absolutely important to demonstrate a deep knowledge of the cases discussed and to focus on the key points.

At the DGRM, sometimes it was difficult for me to analyse the ICSRs sent by the MAH, since the majority of them were very incomplete. Besides many of the fields of the SVIG not being filled and/or being incorrectly filled, the narratives of the cases were most of the times wrongly structured and very confusing, making their comprehension difficult. In fact, at the UFS, I and the other collaborators would make every effort to fulfil all the fields of the PortalRAM, contacting, for that, directly with the reporter. Therefore, when I started my training at the DGRM I found it strange the fact that the ICSRs were received with many fields of the SVIG left blank. In the beginning, I requested the MAH all the information that was not in the fields, but with time and, according to the orientations given by other collaborators of the DGRM, I realised that it was not possible for the MAH to fill in all the fields of the SVIG, since most of the times they cannot have access to all the information on the ADR and, many times, they cannot contact the primary reporter. Hence, I started requesting the MAHs only the essential information that must be present in order to the case being valid.

All these difficulties and challenges were more easily overcome thanks to the help and support given by my colleagues as well as to the good work environment found in both the UFS and DGRM.

5 Conclusion

This report presented my 9 months experience during the curricular training period at the UFS and DGRM of the INFARMED, I.P., describing the activities performed, the hard and soft skills acquired and the learning opportunities achieved.

This training was, undoubtedly, a great experience to me, since it allowed me to involve in a real work environment, applying and improving the knowledge acquired during my Degree in Biomedical Sciences and Master's Degree in Pharmaceutical Biomedicine. I overcame the difficulties found in this training by reading and interpreting the legislation in place and searching for solutions. It was an amazing learning journey, which would not be possible without a good background of theoretical knowledge and soft skills developed during the 5 years of my academic formation.

I consider the objectives defined in the beginning of my training were successfully achieved. I believe that the fact of having my training in two different institutions was an advantage, since it gave me the opportunity to know different people, to work with different teams with different working methods and to understand how two different organisations work. However, there are also some drawbacks of having training in two institutions, since less time is spent in each one. Hence, during the 3 months that I was at the DGRM, I had only a brief contact with the risk minimisation activities and I could not participate in some processes that I would have liked, such as the type II safety variations, RAs and NUIs.

Nevertheless, I truly appreciate what I did during my internship and I believe I made the best of the opportunities I was given. I am really grateful for being granted the opportunity of training in these two institutions and very glad for all the knowledge and lessons that this training provided me.

I would like to stress that this whole experience was so successful largely because of the people that surrounded and supported me throughout my learning path, in my personal and professional growth. Hence, I want to thank the UFS collaborators for all the support, kindness, friendship, and understanding at all times; and also the entire DGRM team for all their teachings, pleasantness and for the willingness to help.

In conclusion, during all this experience I matured and acquired new knowledge and capabilities. At this moment I feel prepared to ingress in the real working world. My objectives for the future are the continuous acquirement of knowledge and improvement of my skills, in order to be able to carry out any work of my interest.

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7 Appendix

A1. Adverse Drug Reaction Reporting Form for healthcare professionals

GOVERNO DE PORTUGAL
MINISTÉRIO DA SAÚDE

SISTEMA NACIONAL DE FARMACOVIGILÂNCIA
Notificação de Suspeita de Reações Adversas a Medicamentos
Profissionais de Saúde

infarmed

Notifique sempre que suspeitar de uma reação adversa — **CONFIDENCIAL**

A. Reação 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 reação adversa (ou o caso, se mais do que uma reação)[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 reação adversa:

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 reação ☐ A reação melhorou após suspensão ☐ Ou manteve-se ☐
Houve redução da posologia (especifique em F.) ☐ Suspeita de interação[4] entre medicamentos (especificar em F.) ☐
O mesmo fármaco foi reintroduzido ☐ Ocorreu reação adversa idêntica aquando da reintrodução ☐
São conhecidas reações anteriores ao mesmo fármaco ☐ São conhecidas reações anteriores a outros fármacos ☐

Considera a relação casual: ☐ Definitiva (certa) ☐ Provável ☐ Possível ☐ Improvável

C. Medicamentos concomitantes, incluindo automedicação (e outo tipo de produtos)

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

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 reação
☐ Cura com sequelas ☐ Desconhecida ☐ Morte com possível relação com a reação

E. Profissional de saúde

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

M-FV-01/03 v.5.ff

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

Para sua maior comodidade, encontra-se disponível em **www.infarmed.pt** o *link* para a nova plataforma de recolha de informação sobre suspeitas de reações adversas a medicamentos: **PORTAL RAM**.

[1] Se for inferior a 1 dia o intervalo de tempo entre a 1.ª administração do medicamento e a RAM, especifique em **F.**
[2] Se ocorreu mais do que uma RAM, considere a gravidade do caso i.e. o conjunto das reações adversas.
[3] No conceito de gravidade, o item "Outra" é utilizado quando a RAM não colocar imediatamente a vida em risco ou resultar em morte, ou em internamento, mas requeira intervenção do profissional de saúde para prevenir que a reação evolua para qualquer um dos outros critérios de gravidade.
[4] Se existir suspeita de interação, considere os respetivos medicamentos como suspeitos.
[5] Mencione os melhores meios de contacto para ser possível a partilha de informação durante o processamento da notificação. Os dados do profissional de saúde notificador são confidenciais.

Para ser considerada válida, uma notificação de reação adversa deverá ter, no mínimo: a informação do profissional de saúde com o meio de contacto; a identificação do doente por iniciais, data de nascimento, idade, grupo etário ou sexo; pelo menos um fármaco/medicamento suspeito e pelo menos uma reação adversa suspeita.

Devem ser notificadas todas as suspeitas de reações adversas graves, mesmo as já descritas; todas as suspeitas de reações adversas não descritas (desconhecidas até à data) mesmo que não sejam graves e todas as suspeitas de aumento da frequência de RAM (graves e não graves).

Entidade	Telefone	Fax	e-mail
Direção Geral do Risco de Medicamentos / INFARMED I.P.	217 987 140	217 987 397	farmacovigilancia@infarmed.pt
Unidade de Farmacovigilância do Norte	225 513 681	225 513 682	ufn@med.up.pt
Unidade de Farmacovigilância do Centro	239 480 138	239 480 117	ufc@aibili.pt
Unidade de Farmacovigilância de Lisboa e Vale do Tejo	217 802 120 / 7	217 802 129	uflvt@sapo.pt
Unidade de Farmacovigilância do Sul	217 971 340	217 971 339	ufs@ff.ul.pt

INVÓLUCRO MENSAGEM

AUTORIZAÇÃO Nº 0048 DE04772010GRC

RSF AUTORIZADO PELOS CTT NO SERVIÇO NACIONAL

ctt correios NÃO CARECE DE SELO

INFARMED, I.P.
Direção de Gestão do Risco de Medicamentos

AVENIDA DO BRASIL 53
1749-970 LISBOA

A2. Adverse Drug Reaction Reporting Form for consumers

Sistema Nacional de Farmacovigilância
Notificação de Suspeita de Reações Adversas a Medicamentos
Utentes

CONFIDENCIAL

Antes de preencher por favor consulte as instruções no verso deste formulário.

*A. DOENTE

Nome (Iniciais): _____ Sexo: M ☐ F ☐ Idade: _____

Data de nascimento: ____/____/_____ Peso (Kg): _____ Altura (cm): _____

*B. REAÇÃO ADVERSA A MEDICAMENTO[1]

1.Descrição	Data de início	Data de fim	Duração

2.Gravidade[2]

Esta situação causou:

- Algum desconforto, mas sem comprometer as atividades diárias habituais ☐
- Desconforto e/ou incapacidade (temporária ou definitiva) no desempenho das atividades diárias habituais ☐
- Desconforto suficiente para recorrer ao aconselhamento/consulta de um profissional de saúde ☐
- O recurso a hospitalização ou o prolongamento da mesma (se já se encontrava hospitalizado) ☐
- Colocou a vida em perigo/risco (segundo opinião médica) ☐
- Malformação à nascença ☐
- Morte ☐

3.Foi necessário efectuar algum tratamento da reação adversa?

Não ☐ Sim ☐ Qual? _____

4.Como evoluiu o estado de saúde do doente?

Cura	☐	Persiste sem recuperação	☐
Cura, mas deixou consequências	☐	Morte	☐
Em recuperação	☐	Desconhecido	☐

5.As reações adversas foram comunicadas a um profissional de saúde?

Não ☐ Sim ☐ Nome e Contacto: _____

*C. MEDICAMENTO SUSPEITO DE TER CAUSADO A REAÇÃO ADVERSA

Nome completo do medicamento _____

Forma farmacêutica (ex.: comprimido, xarope, injetável) _____

Dosagem[3] _____ Nº do Lote (ver embalagem): _____ Via de administração (ex.: oral, injeção ...): _____

Data em que iniciou o medicamento: ____/____/_____ Data em que parou de usar o medicamento: ____/____/_____

Foi a 1ª vez que utilizou este medicamento? Sim ☐ Não ☐

Quantas unidades (ex.: comprimidos, ampolas) do medicamento tomou/utilizou por dia? _____

Para que situação/doença foi utilizado o medicamento? _____

Parou de utilizar o medicamento? Sim ☐ Não ☐ Reduziu a dose ? Sim ☐ Não ☐

Quando deixou de usar o medicamento ou quando reduziu a sua dose, Melhorou ☐ Piorou ☐ Sem diferenças ☐

Para poder notificar uma reação adversa, é necessário fornecer alguns dados pessoais para que possa ser possível contactar o Utente que submeteu a notificação, caso haja necessidade de esclarecimentos adicionais relativamente à mesma. As informações fornecidas serão mantidas seguras e confidenciais, e não serão partilhadas com entidades externas ao Sistema Nacional de Farmacovigilância. Os dados pessoais poderão ser consultados pelo respetivo titular e podem ser objeto de pedido de alteração, no caso de estarem incorretos ou desatualizados.

M-FV-060/01

D. INFORMAÇÃO ADICIONAL
Se tomou/utilizou outros medicamentos, produtos à base de plantas ou suplementos alimentares (nos últimos 3 meses), por favor indique quais:
Outros dados que considere relevantes (alergias, gravidez, resultados de análises ou outros):

*E. NOTIFICADOR
Nome: _____
Morada: _____
Código Postal _____ - _____ _____ Concelho: _____
Telefone: _____ E-mail_____
Data: ___/___/_____ Qual a sua relação com o doente?_____
Assinatura:_____

Obrigado Pela Sua Colaboração

Instruções de preenchimento:

Antes de notificar e sempre que possível fale com um Profissional de Saúde sobre os efeitos indesejáveis sentidos.

Quando iniciar o preenchimento, tenha consigo a embalagem do medicamento e o Folheto Informativo.

Para que a sua notificação possa ser analisada, é indispensável que indique o nome completo do medicamento (mencionado na embalagem ou no Folheto Informativo) e que preencha os quadros A., B. e E. Se possível preencha também com o máximo de informação os restantes campos da ficha.

Explicação das notas numeradas:

[1] Notifique qualquer reação nociva e involuntária, resultante da utilização do medicamento em doses normais, ou resultante de erros terapêuticos, utilização indevida ou abusiva, ou resultante de exposição ocupacional ao medicamento.

[2] Se ocorreu mais do que um efeito secundário, considere a gravidade do conjunto de efeitos secundários e não a gravidade de cada um deles isoladamente.

[3] Na embalagem, junto ao nome do medicamento, está indicada a dosagem do mesmo (ex.: 10 mg; 5 ml).

Para mais informação sobre notificação e sobre o Sistema Nacional de Farmacovigilância visite o *site* – www.infarmed.pt

Entidade	Telefone	Fax	e-mail
DGRM/INFARMED,I.P. Parque de Saúde de Lisboa - Avenida do Brasil, 53, 1749-004 Lisboa	217 987 140	217 987 397	farmacovigilancia@infarmed.pt
Unidade Regional de Farmacovigilancia do Norte Alameda Prof. Hernâni Monteiro, 4 200 - 319 Porto	220 426 952/43	220 426 943	ufn@med.up.pt
Unidade Regional de Farmacovigilancia do Centro Azinhaga de Santa Comba, Celas, 3000 - 548 Coimbra	239 480 138	239 480 117	ufc@sibili.pt
Unidade Regional de Farmacovigilancia de Lisboa e Vale do Tejo Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina de Lisboa, Av. Prof. Egas Moniz, 1649 - 028 Lisboa	217 802 120/7	217 802 129	uflvt@sapo.pt
Unidade Regional de Farmacovigilancia do Sul Av. das Forças Armadas, 1649-019 Lisboa	217 971 340	217 971 339	ufs@ff.ul.pt

A3. CIOMS Form I

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

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

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	

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.)

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

A4. Programme of the XV Course of Practical Pharmacy

ASSOCIAÇÃO DOS ESTUDANTES DA FACULDADE DE FARMÁCIA DA UNIVERSIDADE DE LISBOA

AEFFUL, Av. das Forças Armadas, 1600-083 Lisboa, PORTUGAL
Telefone: +351 217 933 956 Fax: +351 217 968 794 E-mail: geral@aefful.pt
www.aefful.pt Contribuinte n.º: 501 399 968 NIB: 0033.0000.00015339322.06

XV CURSO DE FARMÁCIA PRÁTICA

2 a 11 de Fevereiro de 2013

Faculdade de Farmácia da Universidade de Lisboa
Organizado pelo sub-grupo de Sócio-Farmácia – FFUL e GESP - AEFFUL

2 de Fevereiro de 2013

8h30 – 9h00	**Abertura do secretariado e entrega de documentação**
9h30 – 9h45	**Sessão de Abertura** *António Alfaia, Sub-Director da Faculdade de Farmácia da Universidade de Lisboa* *Pedro Cortegaça, Presidente da DAEFFUL*
9h45 – 10h15	**BLOCO 1** **A – O farmacêutico na indicação farmacêutica e informação sobre medicamentos** *Maria Augusta Soares, Professora FFUL*
10h15 – 10h45	**B – Nutracêuticos** *João Pinto, Professor FFUL*
10h45 – 11h00	*Coffee-Break*
11h00 – 11h30	**C – Terapêutica Inapropriada no Doente Geriátrico** *Maria Augusta Soares, Professora FFUL*
11h30 – 12h00	**D - Contracepção de Emergência** *Gabriela Plácido, Farmacêutica Comunitária*
12h00 – 12h50	**E – O Farmacêutico e o Medicamento Veterinário** *Cláudia Lourenço, Farmacêutica Comunitária*
12h50 – 14h00	**Almoço**
14h00 – 15h15	**F – Princípios e fundamentos da Homeopatia - Aconselhamento farmacêutico** *Ana Luísa Anjos, Farmacêutica Comunitária*
15h15 – 16h00	**G – Nova Legislação da Farmacovigilância** *Alexandra Bernardino, Unidade de Farmacovigilância do Sul*

AEFFUL, Av. das Forças Armadas, 1600-083 Lisboa, PORTUGAL
Telefone: +351 217 933 956 Fax: +351 217 968 794 E-mail: geral@aefful.pt
www.aefful.pt Contribuinte n.º: 501 399 968 NIB: 0033.0000.00015339322.06

Dias de Workshops – 4, 5, 7 e 8 de Fevereiro de 2013

Bloco 2	
A – Constipação, Gripe, Febre e Congestão Nasal	*Paula Cerqueira Afonso*
B – Tosse, Dores de Garganta e Rouquidão	*Nuno Saramago / Fátima Baião Santos/ Fátima Duarte Ramos/ Graça Campos*

Bloco 3	
A - Dermatites (incluindo a das Fraldas, Psoríase, Caspa e Acne)	*Rute Ferreira/ Marta Brito/Raquel Roma*
B – Micoses, Ectoparasitoses e Herpes Labial	*Graça Campos/ Rui Valente*

Bloco 4	
A – Aftas, Epigastralgias, Indigestão e Hemorroidas	*Margarida Pinto/ Alexandra Alves*
B – Diarreia, Obstipação e Parasitoses Intestinais	*Lúcia Rocha/ Rute Miranda*

Bloco 5	
A – Aconselhamento ao doente: abordagem prática	*Isalinda Bastos/ Fátima Baião Santos*
B – Farmacovigilância – abordagem prática	*Paula Barão/ Ana Tereza Neres/ Alexandra Bernardino,* Unidade de Farmacovigilância do Sul

Horário dos Workshops
09:30 – 11:00 – Resolução de casos práticos
11:00 – 11:15 – Intervalo
11:15 – 12:00 – Apresentação teórica
12:00 – 12:30 – Discussão conjunta

12:30 – 14:00 – Intervalo para almoço

14:00 – 15:30 – Resolução de casos práticos
15:30 – 15:45 – Intervalo
15:45 – 16:30 – Apresentação teórica
16:30 – 17:00 – Discussão conjunta

A5. Lecturer Certificate at the XV Course of Practical Pharmacy

Lisboa, 2 de Fevereiro de 2013

Exma. Drª. Alexandra Bernardino,

O ***Gabinete de Estágios e Saídas Profissionais*** *(GESP)*, da Associação dos Estudantes da Faculdade de Farmácia da Universidade de Lisboa, vem, por este meio, demonstrar a sua gratidão com a participação de V. Ex.ª como Oradora no **XV Curso de Farmácia Prática**, realizado na Faculdade de Farmácia da Universidade de Lisboa, e que se revelou, sem dúvida, um enorme complemento para a formação dos nossos alunos, conferindo-lhes algumas valências essenciais como futuros profissionais de saúde.

Desejamos que esta actividade tenha constituído uma positiva experiência para V. Exª, tal como foi, com certeza, para todos os participantes.

Contando com a sua presença para dignificar futuras acções da Associação dos Estudantes, endereçamos-lhe os nossos melhores cumprimentos.

Atenciosamente,

P'lo GESP – DAEFFUL,

A.E.F.F.U.L
Av. Professor Gama Pinto
1649-003 Lisboa
Contribuinte : 501 399 968
Tel. +351 217 933 956
Fax. +351 217 968 794
geral@aefful.pt
www.aefful.pt

(Ana Rita Cunha

Pedro Pissarra Luís)

A6. "Tools for Managing Bibliographic References" Workshop Certificate

iMed.UL
RESEARCH INSTITUTE FOR MEDICINES AND PHARMACEUTICAL SCIENCES

ipSC
iMed.UL POST-GRADUATE STUDENTS COMMISSION

FACULDADE DE FARMÁCIA
Universidade de Lisboa

This certifies that

Alexandra Bernardino

attended the Workshop from *i*Med.UL Post-Graduate Students Commission, "**Ferramentas de Gestão de Referências Bibliográficas**" that was held at the Faculty of Pharmacy, University of Lisbon on February 27th 2013.

On behalf of the Executive Committee of iMed.UL,

A7. "CVs and Motivation Letters" Workshop Certificate

A8. I Post-Graduated Course in Good Clinical Practices Certificate

FACULDADE DE MEDICINA DA UNIVERSIDADE DE LISBOA

INSTITUTO DE FORMAÇÃO AVANÇADA

CERTIFICADO

Certifica-se que **Alexandra Filipa Bernardino** esteve presente no I **Curso Pós-Graduado de Actualização BOAS PRÁTICAS CLÍNICAS**, que decorreu nos dias 22 e 23 de Maio de 2013, no Edifício Egas Moniz da Faculdade de Medicina da Universidade de Lisboa. O Curso teve a duração de 11 horas.

Prof. Doutor Joaquim Ferreira

Director do Curso