Engrácia Maria Santos Nobre

The Criteria for evaluating the Pharmacovigilance System in Belgium, Canada, Holand and Portugal

Monografia realizada no âmbito da unidade de Estágio Curricular do Mestrado Integrado em Ciências Farmacêuticas, orientada pelo Professor Doutor Francisco Batel Marques e apresentada à Faculdade de Farmácia da Universidade de Coimbra

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Coimbra, 15 de julho de 2016.

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(Engrácia Maria Santos Nobre)

Os meus sinceros agradecimentos...

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Abbreviations

ADR – Adverse Drug Reaction

BCPH – The Belgian Centre for Pharmacovigilance for Medicine for Human use

DGRM – The unit of Risk Management of Medication

EEA – European Economic Area

EMA – European Medicine Agency (The Agency)

EU – European Union

FAMPH – The Federal Agency for Medicine and Health Products

FDA – The American Food and Drug Administration

GVP – Guidelines on Good Pharmacovigilance practices

IGZ – The National Health Care Inspectorate

ISO – International Organization for standardization

MAH – Marketing Authorization Holder

MEB – The Medicine Evaluation Board

MHRA – The Medicines and Healthcare Product Regulatory Agency

NPC – National Pharmacovigilance Centre

NPS – National Pharmacovigilance System

PDCA cycle – Plan, Do, Check, Act cycle

TGA – The Australian Therapeutic Goods Administration

TQM – Total Quality Management System

WHO – The World Health Organization

Abstract

Throughout the years the importance of pharmacovigilance has grown and it has become necessary that the competent authorities have a well-established pharmacovigilance system. It is required inorder to guarentee the quality of life of every person that is directly or indirectly involved with medicine. The purpose of such pharmacovigilance system is to reduce the risk and increase the benefits of medicine. Therefore it is extremely important to ensure the quality of such systems. The present thesis has as its goal to explore the pharmacovigilance systems in Belgium, Canada, holland and Portugal and to identify which "performance indicators" are used to evaluate the quality of each pharmacovigilance system.

Keywords:

Pharmacovigilance; quality of pharmacovigilance system; performance indicators.

Resumo

Ao longo dos anos, a importância da farmacovigilância tem evoluído e tem-se tornado necessário que as autoridades competentes dispõem de um sistema de farmacovigilância bem estabelecida para tranquilizar a qualidade de vida de cada pessoa que está diretamente ou não envolvidos com fármacos. A finalidade de tal sistema de farmacovigilância é reduzir o risco e aumentar os benefícios dos medicamentos. Por isso, é extremamente importante assegurar a qualidade de tais sistemas. Este trabalho tem como objetivo explorar os sistemas de farmacovigilância da Bélgica, Canadá, Holanda e Portugal e identificar quais os "indicadores de desempenho" utilizados para avaliar a qualidade de cada sistema de farmacovigilância.

Palavras-chave:

Farmacovigilância; Qualidade do sistema de farmacovigilância; indicadores de desempenho.

1. Introduction

Pharmacovigilance is defined as the science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems. Pharmacovigilance activities include: collecting and managing data on safety of medicines; looking at the data to detect "signals"; evaluating the data and making decisions with regards to safety issues; pro-active risk management to minimise any potential risks associated with the use of the medicine; acting to protect public health; communicating with and informing stakeholders and public; and audit, both of the outcomes of action taken and of the key processes involved ("The EU pharmacovigilance system," 2014). Bassically it involves the systematic collection, collation and analysis of reports of suspected adverse drug reactions (ADR) enabling detection of signals, their communication and risk management (WHO, 2015). The process of pharmacovigilance is represented schematicaly in figure 1 in the annex. Only in the 1960s was it deemed necessary to closely control de quality, efficacy and safety of medicines before making the medication available. At the time it became apparent that the medicine thalidomide was causing congenital disorders among children whose mothers had used the medicine during pregnancy. This led to a global awareness that medicines can produce unexpected adverse effects (famph, 2011c). Throughout the years it has become clear that the process of evaluating drug safety has to continue even after marketing autorization due to the lack of safety information aquired during the pre-marketing phase. Not only is this the responsability of the marketing authorization holders (MAH), but also of the competent authorities and the Agency (EMA) (World Health Organization WHO, 2002).

To perform any pharmacovigilance activities, it is necessary to establish a pharmacivigilance system. A pharmacovigilance system is defined as a system used by an organization to fulfill its legal tasks and responsabilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detects any changes to their risk-benefit balance. A pharmacovigilance system, like any system, is characterized by its structures, processes and outcomes. The quality of a pharmacovigilance system can be defined as all the caracteristics of the system, which are considered to produce, according to estimated likelihoods, outcomes relevant to the objectives of pharmacovigilance. Pre-defined quality requirements, which are characteristics of a system that produce the desired outcome, are necessary to measure quality. The overall quality objectives for pharmacovigilance systems are: complying with the legal requirements for pharmacovigilance tasks and responsabilities; preventing harm from ADRs; promoting the safe and effective use

of medicinal products by providing timely information about the safety of medicinal products; and contributing to the protection of patients and public health. The process to monitor the performance and effectiveness of a pharmacovigilance system and its quality system should include reviews of the systems, audits, compliance monitoring, inspections and evaluating the effectiveness of actions taken with medicinal products for the purpose of minimising risks and supporting their safe and effective use. The organization may use performance indicators to monitor continously the good performance of pharmacovigilance activities in relation to the quality requirements. (GVP module I). Pharmacovigilance indicators are measures of inputs, processes, outputs, outcomes, and impacts of development projects, programmes or policies related to health systems and services. The main objective of the pharmacovigilance indicators is to provide measures that will enable the assessment of the status of pharmacovigilance, the activities and their impact, globally at all levels of the health-care system, with a view to ensuring patient safety (WHO, 2015).

The present work has the purpose to decribe how the pharmacovigilance system works and how the quality of the pharmacovigilance system is evaluated in Belgium, Canada, Holland and Portugal. This paper will discuss each pharmacovigilance system separately. First of all it will discuss which competent authority is responsable for the pharmacovigilance in the country and then it will adress how and who evaluetes the system in each country. This will demonstrate if there is a standard pattern in the evaluation of the quality of the pharmacovigilance systems in the world.

2. Belgium

2.1 Introduction

The Federal Agency for Medicines and Health Products (FAMHP) was created in 2007 and is the competent authority for the quality, safety and efficacy of health products that are in clinical development and on the market. The FAMPH works together with health professionals and other competent authorities at the national and international level to ensure the population of Belgium the optimal use of the medicines and health products. In terms of vigilance the FAMPH supervises the adverse effects due to the use of medicines or health products by collecting information. Information is gathered and evalueted and, if necessary, measures are taken (famph, 2015).

The Belgian Centre for pharmacovigilance for medicines for Human use (BCPH), a subunit of the FAMPH, started its activities in 1976 and is responsible for coordinating the diferente tasks related to pharmacivigilance. These tasks include: collecting

pharmacovigilance data; evaluating the pharmacovigilance data; and if required taking action. The BCPH is part of a European network of pharmacovigilance, called Eudravigilance (famph, 2011a). Eudravigilance is a data processing network and management system for reporting and evaluating suspected ADRs during the developmet, and following the marketing authorisation of medicinal products in the European Economic Area (EEA) (EMA, 2007). The BCPH takes part in the evaluation of pharmacovigilance data for medicines that are authorized through a European procedure. The main tasks of the BCPH are: collecting and evaluating individual reports of adverse effects coming from healthcare professionals and marketing authorization holders; collecting and evaluating periodic safety reports; collecting and evaluating reports about safety of patients during clinical trials involving medicines authorized in Belgium; participating in European pharmacovigilance activities; distributing information about pharmacovigilance to healthcare professionals and the general public; implementing the proposed measures following the evaluation of the pharmacovigilance data; and evaluating risk management plans and pharmacovigilance systems (famph, 2011a). Since December 2010, health professionals can report ADRs not only by filling in the yellow card and sending it by post but they can also submit and ADR online via www.fichejaune.be (famph, 2011b)

2.2 How the pharmacovigilance system is evaluated

The FAMPH believe that an efficient quality management system is an importante tool to show that the diverse and complex tasks are being executed in the correct way, observing all regulations in effect. It is important on a national scale but also on an international scale. The mutual recognition of quality based on quality labels is essential to allow competente medicines authorities within the European Union (EU) to put confidence in each other. The FAMPH works with a Total Quality Management system (TQM). This implies that they choose a transversal cross-pilar approach, involving all pillars, departments, divisions and smaller entities of the FAMPH, to strive for quality improvement continuously. This system makes use of a PDCA-cycle (Plan-Do-Check-Act). A quality management cycle by definition implies that one analyses one´s activities at regular intervals in order to identify points for improvement. Not only does the FAMPH have the TQM system to evaluate the performance of the organization but also the government demands the realization of a functional internal control and internal audit service within the federal public services. The internal audit system has to be organized independently and is meant to reveal strength and weaknesses and find opportunities and threaths (Offshore, 2010).

The entry into force of the new legislation on pharmacovigilance in July 2012, established legal requirements for competente authorities in the Member States, The Agency and the MAH to perform audits of their pharmacovigilance systems, including risk based audits of their quality system. This means that the FAMPH has audits executed by the government to assess their overall performance as an organization as well as at the level of their pharmacovigilance system. The audits realized to evaluate the pharmacovigilance system are based on module IV of "The guidelines on good pharmacovigilance practices" (GVP). This module provides guidance on planning and conducting the legally required audits, and in respect of the operation of the EU regulatory network, the role, context and management of pharmacovigilance audit activity. This module is intented to facilitate the performance of pharmacovigilance audit, especially to promote harmonisation, and encourage consistency and simplification of the process. In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criterias are fulfilled, contributing to the improvement of risk management, control and governance processes. In the context of the pharmacovigilance, audit criteria should reflect the requirements for the pharmacovigilance system, including its quality system for pharmacovigilance activities, as found in the legislation and guidelines. It is important to mention that these audits should be independent to make sure that there are no interference with the results (States, Draft, & Start, 2012). In conclusion, the FAMPH is obligated to performe risk-based audits of the quality system as well, at regular intervals according to common methodology to ensure that the quality system complies with the requirements. The results of the audits are reported to the Agency regularly.

Literature does not refer which performance indicatores are used to evaluate the pharmacovigilance system in the FAMPH. It only states that the organization follows the legislation and guidelines.

3. Canada

3.1 Pharmacovigilance in Canada

The Canada Vigilance Program is Health Canada´s post-market surveillance program that collects and assesses reports of suspected adverse reactions to health products marketed in Canada. The program has collected reports of suspected adverse reactions since 1965. ADRs are submitted by health professionals and consumers either directly to Health Canada or via MAHs. This can be done online, by phone or by submitting a reporting

form by fax or by email. Health Canada´s lifecycle approach to health products vigilance can be seen in figure 2 in the annex. The information collected can be accessed through the Canada Vigilance Online Database (Government of Canada, Health Canada, Health Canada, Health Products and Food Branch, Marketed Health Products Directorate, 2016). This information is one of the tools that enables Health Canada to monitor the safety profile of health products to determine if their benefits continue to outwheigh their risks. Consumers, health professionals, MAH and the general public can view the types of adverse reactions that have been reported to Health Canada via the Canada Vigilance Adverse Reaction Online Database, which contains over 225,000 reports that have occured in Canada since 1965 (*Canada Vigilance Program — Collecting and Assessing Adverse Reaction Reports MedEffect Canada MedEffet Canada*, 2011).

Seven Canada Vigilance Regional Offices provide local points of contact for health professionals and consumers to support the Canada Vigilance Program. Adverse reaction reports are collected regionally and forwarded to the National Office for further analysis. MAH send reports directly to the National Office (*Canada Vigilance Program — Collecting and Assessing Adverse Reaction Reports MedEffect Canada MedEffet Canada*, 2011).

The MedEffect Canada was created in 2005 to improve acess to new safety information and adverse reaction reporting as well as to provide a single window approach to post-market surveillance activities and programs related to health products marketed in Canada. The objectives of the MedEffect are to provide centralized access to new safety information, address the requirement to make it as simple and eficiente as possible for everyone, increase awareness about the importance of reporting adverse reactions and identify the needs of target audience for post-market surveillance activities. This initiative is key to the involvement of the public in supporting an effective post-market surveillance program. MedEffect Canada helps maximize the safety of health products in the Canadian market by reaching out to key public audiences by building awareness about the importance of reporting ADRs, facilitating access to a centralized network to stay informed, and making access easier for MAH to guidence and consultative documents, legislations and Acts (Undertaken, We, & Improve, 2005a). The key aspects of the post-market surveillance program and supporting elements of MedEffect Canada can be found in figure 3 in the annex. The government of Canada is making more data and information available to Canadians than ever before, this includes all information about pharmacovigilance (Government of Canada, 2016). The Canadian Government also has guidelines that anyone can consult on what, how, who and when to report an ADR.

3.2 How the pharmacovigilance system is evaluated

Canada looks to and collaborated with regulatory counterparts suchs as the EMA, the Medicines and Healthcare Product Regulatory Agency (MHRA), the American Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) for information and partnership on product vigilance activities (Government of Canada, 2012). Health Canada has developed guidelines on good pharmacovigilance practices thanks to the information received from the authorities previously mentioned (Government of Canada, 2005). These guidelines help the population to fully understand ADRs and the importance of reporting such ADRs. They also help MAH to uphold legislation. All of this helps the vigilance program and the MedEffect initiative to performe better and guarantee quality.

The pharmacovigilance system in Canada is not directly evaluated but instead Health Canada is evaluated as a whole. Federal departments are required to report plans and performance results to demonstrate accountability for the funds received vis-à-vis the programs and services delivered. The focus of the audit is departamental performance reporting. Quality reporting of both financial and non-financial information provides an importante input into management´s decision-making processes and strengthens public acountability. The objective of the audit is to provide assurance that the governance, risk management and controls related to Health Canada performance reporting are adequate and effective (Bureau, 2013).

The Targets of Health Canada and its pharmacovigilance system are: to enhance capacity of Health Canada and the pharmaceutical industry to identify and respond to risk issues; increase capacity to identify safety issues with health products on the market; increase knowledge of post-market drug safety and effectiveness; and improve ability to monitor and control importation of health products. The performace indicatores used to evaluate if the objectives of the Health canada and subsequentely the pharmacovigilance system are being fulfilled are: year-over-year increase in PSUR submitted by industry; number of new safety signals generated through PSUR reviews per year; percent of safety issues identified by MAH; percent of ADRs addressed within servisse standards; number of import alerts resulting in detecting/stopping non-compliant products at the morder; and number of health products admissibility determinations that recommend refusal of entry into Canada (Government of Canada, Treasury Board of Canada, Secretariat, 2015).

On the contrary of Belgium, Canada has all of the information available for the public due to Regulatory Transparency and Openness Framework. This makes more data and

information available to Canadians so that the population can participate in discussions on government policies and priorities (Government of Canada, 2016).

4. The Netherlands

4.1 Pharmacoviglance in the Netherlands

The medicines Evaluation Board (MEB), created in 1963, assesses and monitors the efficacy, risks and quality of human and veterinary medicines, and the safety of novel foods for human consumption. The MEB is an idependent administrative body residing under the government of the Netherlands (Ministery of Health, Welfare and Sport). This means that the organization decides independently about the authorisation and monitoring of human medicinal products(CBG-MEB, n.d.). The MEB is made up of various organization and units, one of them being the pharmacovigilance unit (CBG, 2016). This unit evaluates safety information on authorised medicines. Figure 4 of the annex shows some of the procedures that the organization did in 2015. The unit has close contact with the Netherlands Pharmacovigilance Centre LARED, which, with the use of its database and that of the EU, continouosly monitors potential safety problems of medicines (CBG, n.d.-c).

Lareb is an independente Foundation that is assigned by the MEB to collect and assess reports of ADR received from healthcare professionals, patients and the MAH. They can report on a paper form or via de reporting form on their Dutch website. Any reported ADR of medicines is carefully analysed by Lareb and is stored at a central collecting point. This is how Lareb can monitor the safety of medicines in the Netherlands. Lareb works independently and gives importante reports of ADR anonymously to the MEB (Lareb, n.d.-a). In 2003, the Netherlands became one of the first countries in the world to allow patients to report ADRs. After a report is received, a pharmacist or physician will assess it. In a weekly signal detection meeting the reports are reviewed on a case-by-case basis. Statistical techniques are used to support the signal detection process. On a quartely basis, the signals are forwarded to the Dutch Medicines Evaluation Board where it is decided if further action is necessary. The reports are subsequently filled into their database and an anonymous copy is sent on a weekly basis to the Eudravigilance database and the WHO (World Health Organization) collaborating center for International Drug Monitoring in Uppsala (Sweden) (Lareb, n.d.-b). In 2013 Lareb was appointed WHO collaborating Centre for Pharmacovigilance in Education and Patient Reporting. As a collaborating Centre Lareb wants to serve as a platform for knowledge transfer by providing training, conducting

research and developing best practice for staff active in pharmacovigilance, both at national centres as well as in academia (Lareb, 2013).

4.2 How the pharmacovigilance system is evaluated

The MEB is an independente administrative body under the auspices of the central government. This mean that the MEB makes independente decisions on the authorisation and monitoring of medicinal product (CBG, n.d.-a). This also means that the organisation is evaluated by the Minister of Health, Welfare and Sports. On behalf of the Minister of Health, Welfare and Sports, the Government Audit Department and the Finacial and Economic Affairs Department monitors the quality of the MEB´s organisation and operation, and also monitors the efficient and legitimate deployment of funds (CBG, n.d.-b).

The MEB has a Quality Control Committee that uses notifications and reports as a starting point to evaluate how well the organisation responds to identified flaws and issues. Where necessary, the committee makes suggestions for improvement and monitors the follow-up. The committee is independente and reports to the executive of the MEB (Medicine Evaluation Board, 2015).

The MEB was the first European authorisation agency to have its quality management certified (CBG, 2015). The organisation has had an ISO (International Organization for Standarization) certification for many years and has been recertified in 2015. ISO 9001 is the internationally accepted standard for quality management systems. It presents the criteria for a quality management system that can be used by an organisation to improve customer satisfaction by meeting the customer's requirements and conforming to the relevant legislation (Medicine Evaluation Board, 2015). The audit that was done to meet ISO 9001:2008 revealed that the MEB has access to a very thorough quality management system which is evidenced by clear plans, good monitoring and adequate assessment and guidence. The audit evaluated the policies, organisation, primary processes, results, people and resources of the MEB (Board, 2015).

The work processes of the MEB are strictly regulated by national and international legislation and regulation. In accordance with Article 101 (2) of the Directive 2001/83/EC it is mandatory for member states to performe regular audits of their pharmacovigilance system and to report the results to the European Commision (CBG, 2015). The inspection tasks are performed by the National Health Care Inspectorate (IGZ). The IGZ promotes public health through effective enforcement of the quality of Health services, prevention measures and medical products. The detailed operational requirements of all the MEB pharmacovigilance tasks that contitute the MEB´s pharmacovigilance system are set out in

the MEB´s policies, standard operating procedures and work instructions, which are part of the MEB´s integrated quality management system (ISO 9001 certification). The pharmacovigilance system is embedded in the overall quality system which for exemple also takes into account the startegy, governance, and bussiness and resource planning of the MEB and all the licensing activities. Performance is monitored in several ways and at diferent levels. At the operational level peer review mechanisms are in place for pharmacovigilance processes within the pharmacovigilance division, but review also takes place through discussion of report in meeting with the board. After each meeting the board gives feedback on the quality of the reports and the discussion being held. At the bussiness level several management reports are available at the department level, at the process/ procedure level, and at the individual level. The results of the audit sent to the European commision shows that the pharmacovigilance system of MEB is according to national and international legislation (Board, 2015).

The performace indicatores are not indicated in literature. Literature just refers that the MEB follows all the legislation and that the quality of the pharmacovigilance system upholds to legislation and guidelines.

In 2008 Lareb started taking measures to introduce a quality system according to the ISO standards. In March 2009 Lareb achieved the ISO 9001.2000 certificate. Like it was done for MEB, the organisation responsible for the certification investigated Lareb´s policies, organization, processes, results, employees and cooperation /automation. They also checked if the pharmacovigilance system was according to the PDCA-cycle (E.P. Van Puijenbroek, 2009). The PDCA-cycle is demonstrated in figure 5 in the annex. The PDCA cycle is not one of the ISO 9001 Standard requirements, but it is an efficient tool for achieving its requirements (Itah Abuhav, 2014).

Throughout the whole research about the pharmacovigilance system in the Netherlands nothing was found about performace indicators.

5. Portugal

5.1 Pharmacovigilance in Portugal

The National Pharmacovigilance System (NPS) was created in 1992 and has been evolving to meet the current needs. The system was established in a centralized manner, but it soon became clear that a geographic decentralization would bring more advantage in terms of proximity of the system to health professionals as well as the involvement of the universities. Over these 24 years, the NPS has been adapting to the EU requirements in the

area of pharmacovogilance, and is currentely a mature and well implemented system, with the objectives to evaluate the safety profile of marketed drugs and estabelishing measures to reduce the risks of these drugs (Herdeiro, 2012).

On the contrary of other countries in the EU, Portugal didnt have a pharmacovigilance system up until the beginning of the 1990s. The first importante step was taken in 1991 with the publication of the so-called Statute Of The Drug (Decree-law 72/91 of February 8) setting new standars for drugs for human use. The decree mencioned pharmacovigilance for the very first time and it stated that the pharmaceutical industry and health profesionals should sent to the health authorities reports of ADRs (Pina & Corrêa-Nunes, 1998).The implementing order 107/92 of 27.06.92 announced de creation of the NPS as well as the National Pharmacovigilance Centre (NPC). The National Authority of Medicines and Health Products (Infarmed), formerly known as National Institute of Pharmacy and Medicine emerges in 1993 by decree-law No. 10/93 of 15.01.93. Four Regional units of pharmacovigilance were created in 2000: the northern pharmacovigilance unit; the southern pharmacovigilance unit; the pharmacovigilance unit of the Azores (inactive); and the core pharmacovigilance unit of the centre. The NPS becomes thus a decentralized system, approaching health professionals, involving universities to promote their technical and scientific expertise, diffusing the system and increasing the notification. In 2003, there was a reorganization at the level of the Southern pharmacovigilance unit which became the pharmacovigilance unit of Lisbon and Tagus Valley, and also the emerging of a new regional unit: the southern pharmacovigilance unit. In 2006, the Decree-Law 176/2006, of 30.08.06, was approved unifiying the laws of human use medicine. The drug surveillance relies mostly on spontaneous reporting of ADR made by the health professionals to the national authority by pre- filling an online form, on paper (sent by mail, fax or e-mail) or by phone. In Portugal, the spontaneous reporting ADR has evolved favorably, approaching the value of 200 reports / million inhabitants recommended by WHO, which puts the country in an active position with regard to this matter (Herdeiro, 2012).

5.2 How the pharmacovigilance system is evaluated

The entity responsible for evaluating the performance of the pharmacovigilance system is the Infarmed, but more precisely its subdivion the Risk Management of Medication department (DGRM). The DGRM with the help of its unit that is responsable for the management of the NPS coordinates, monitors and regulates the NPS. The DGRM is also responsible for the participation in the European pharmacovigilance network and for the management of the alert system (Infarmed, 2011).

Each regional unit has to fill in a form like the one that is shown in the annex II. The services and the indicators set out in the form relate to the objectives and time limits for the activity to be undertaken by the regional unit. In the form you can find basic data of the pharmacovigilance unit, activities of processing and analysis, specific communication activities with Infarmed, and additional activities done by the regional unit. The performance indicatores are established in the form for each service done by the regional unit. Some of these performance indicatores include total number of spontaneous reports received, validated, classified and registered; number of reporting physicians/ nurses/ pharmacists; and number of spontaneous reports with causality assessment. The form also establishes the targets that should be achieved by the regional pharmacovigilance unit. This is how the Infarmed can evaluate if the pharmacovigilance system is performing adequately or not.

Infarmed also publishes every trimester the notifications and ADR cases that were sent by health professionals and by the public to the regional units. The organization also publishes an anual report of every notification of ADRs that was received throughout the year which can be found on the website of the Infarmed.

The pharmacovigilance system of Portugal, like the others, upholds to national and international legislation and guidelines.

Conclusion

Pharmacovigilance and all drug safety activities are relevant for anyone that comes in contact in any way with medication. The ultimate goal of pharmacovigilance is to guarantee patient protection and public health. Over the years, pharmacovigilance has changed to guarantee such safety. These changes can be found in the legislation and guidelines.

Throughout the research for this work, it has been very clear that all the pharmacovigilance systems are acording to the national and international legislation. Each country is evolving their pharmacovigilance system so that they can improve overall health and wellbeing of their citizens and to minimize the risks of medication. Besides following the current legislations and guidelines, some of the organizations responsible for pharmacovigilance have had their quality management certified, like for example the MEB and Lareb in the Netherlands.

This research also demonstrated the lack of information in the literature about the performance indicators used to evaluate the pharmacovigilance system of each country. This information is important to understand if the evaluation of the pharmacovigilance systems is based on a standard pattern. Using a standard pattern for the evaluation can improve harmonization throughout the whole world. This would only bring benefits for everyone. It would make information more accessible and would improve the safety of medication. This could be an area that should be explored so that all pharmacovigilance systems work in the same way with the same quality under the same aims.

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Annex I

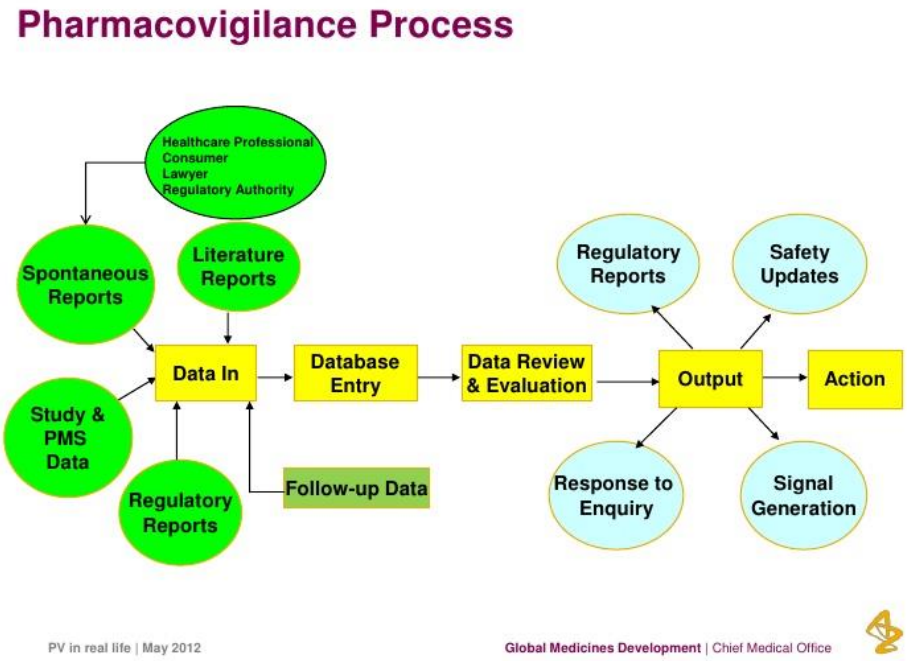

Figure 1 – Schematic representation of the process of pharmacovigilance (Astrazeneca, 2012).

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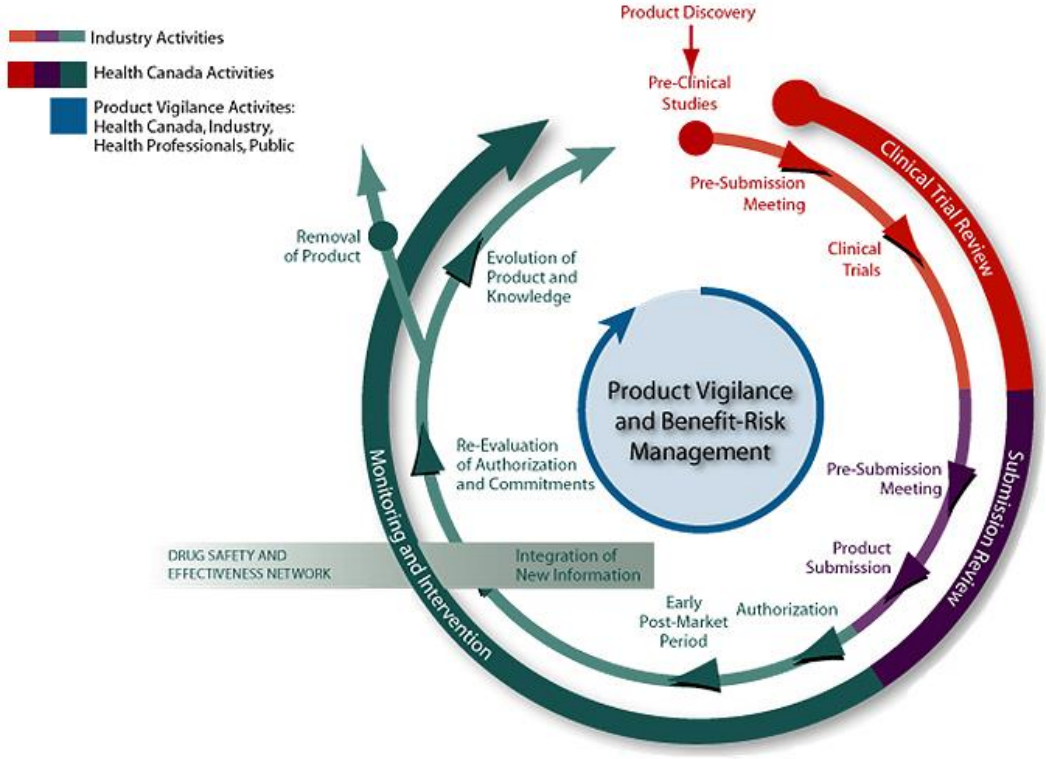

Figure 2 – Health Canada´s lifecycle approach to health products vigilance (Government of Canada, 2012).

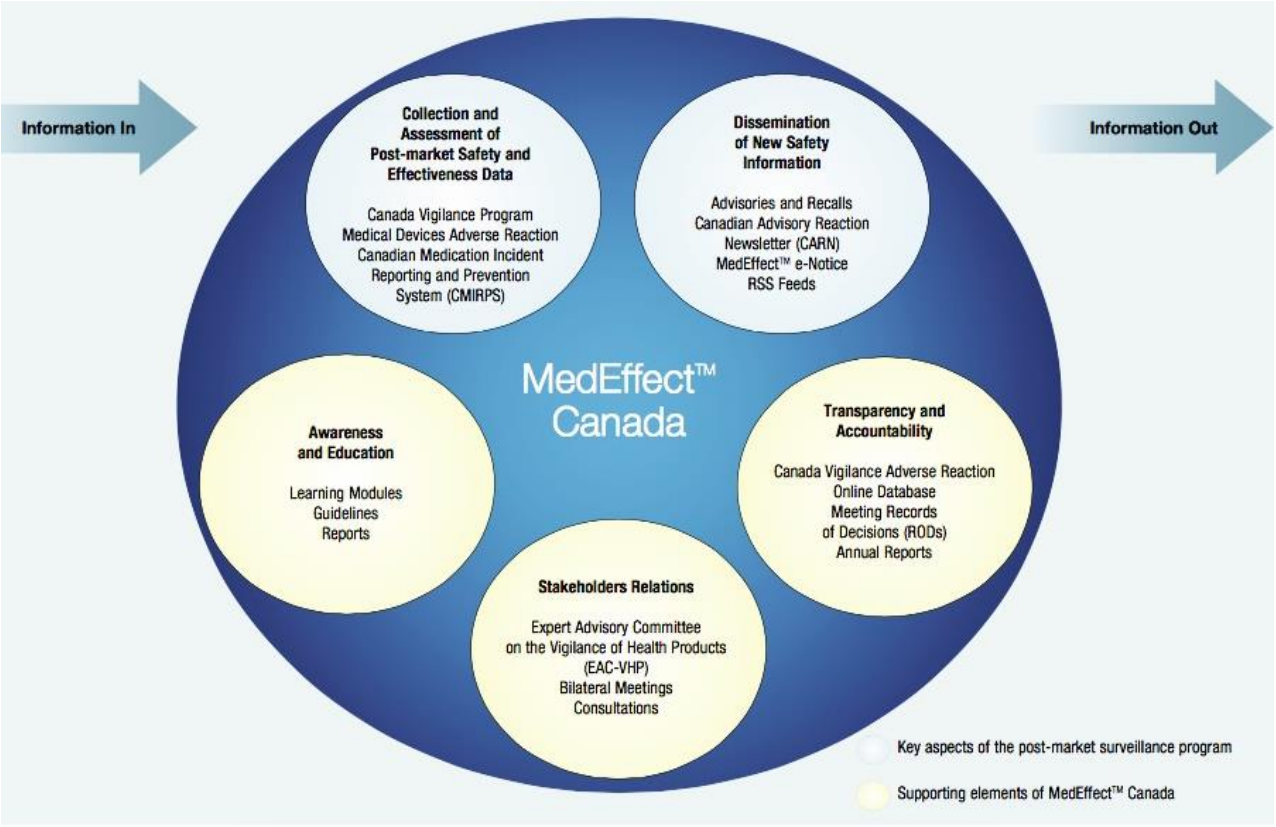

Figure 3 - The key aspects of the post-market surveillance program and supporting elements of MedEffect Canada (Undertaken, We, & Improve, 2005b).

National activities/assessments	**Quantity**
Lareb signals discussed in Board meetings	14 (separate discussions from July 2015 onwards)
Implementation of additional risk-minimisation measures	80
European activities/procedures (NL = rapporteur)	
Assessment of protocols for Post Approval Safety Study (PASS)	18
Assessment of PSUR Single Assessment (PSUSA)	61
Signal management*	18*
Lead Member State for monthly signal detection (number of substances)	52

* Signal management: the entire process covering the identification of new risk information, its processing and assessment, including making recommendations about follow-up action (e.g. revising product information) and the associated communication.

Figure 4 – Procedures that were done by the MEB in 2015 (Medicine Evaluation Board, 2015).

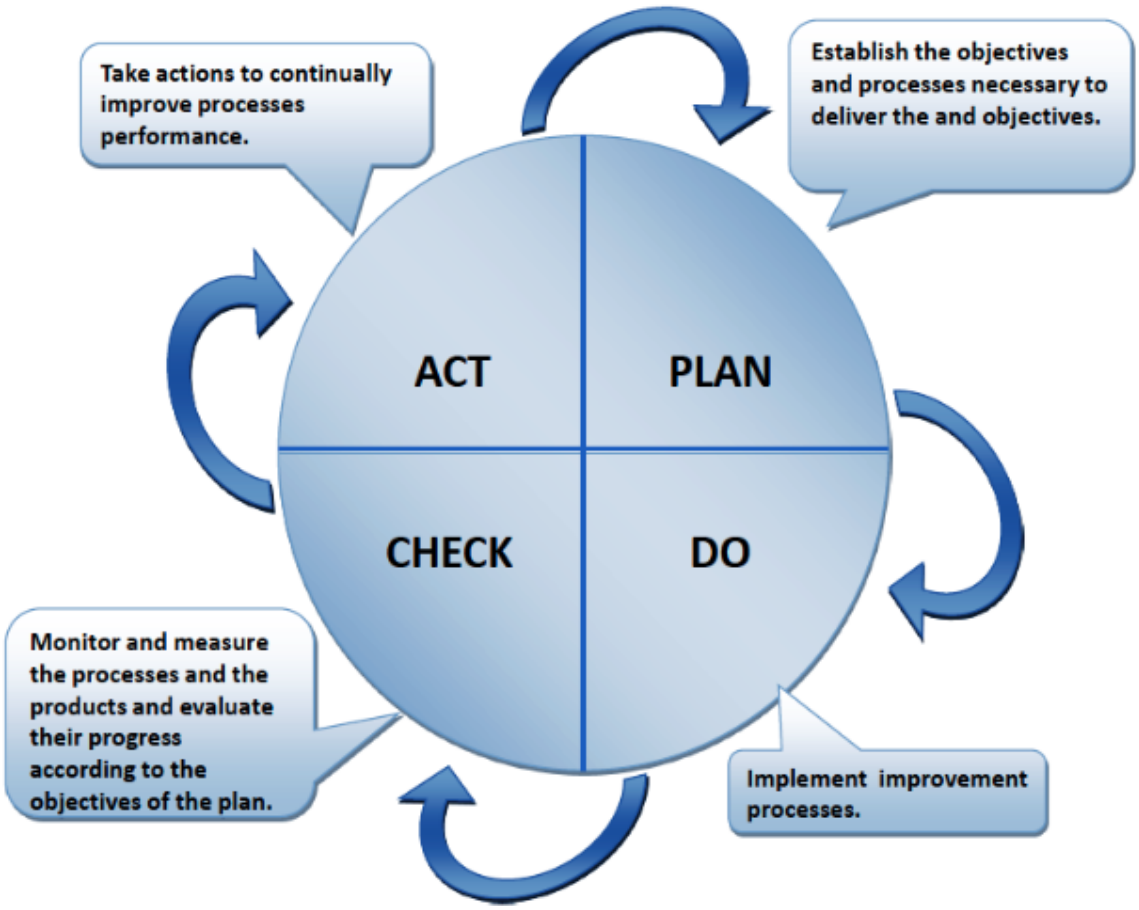

Figure 5 – Diagram representing praphically the PDCA process and its continual process (Itah Abuhav, 2014).

Annex II

Form that the Regional Units of Portugal fill and send to the Infarmed.

Basic data of Pharmacovigilance unit

Name of Regional Pharmacovigilance Unit	
Geographic region	
Population	
Area in km^2	
Number of physicians in the region	
Number of pharmacists in the region	
Number of nurses in the region	
Number of spontaneous reports foreseen in the protocol , per year and per million inhabitants	

Activities of Processing and Analysis			
Reception, classification, processing and validation of spontaneous reports of suspected adverse reactions, including causality assessment, and assurance of data confidentiality, by following the standard operating procedures (SOPs) in force			
Activity		Results	
Total n° of spontaneous reports received, validated, classified and registered			
N° of spontaneous reports received and classified as serious			
N° of spontaneous reports received and classified as unknown (not described in SPC*)			
N° of spontaneous reports received and classified as non-serious			
N° of reporting physicians			
N° of reporting pharmacists			
N° of reporting nurses			
N° of other health professionals reporting suspected ADRs			
N° of reporting patients/consumers			
Total n° of reporters			
N° of spontaneous reports with causality assessment			
N° of spontaneous reports with causality			

assessment processed in the database within 30 days			
N° of assessment reports about possible safety signals issued by the Regional Pharmacovigilance Unit (RPU) and sent to the Coordinator of the Pharmacovigilance System (CPS)			
Total number of assessment reports about safety signals requested by the CPS and issued by initiative of the RPU			
Total number of spontaneous reports that could arise a possible safety signal			
Number of assessment reports about possible quality signals sent to the CPS, according to the SOPs in force			
Total number of assessment reports of possible quality signals issued by the RPU			
Main indicators	**Target**	**Results**	**Achievement**
1. Reporting rate of ADR			
2. Rate of serious ADR			
3. Rate of ADR with causality assessment			
4. Rate of ADR with causal assessment within the time limit			
5. Rate of assessment reports about possible safety signals			
6. Rate of assessment reports on possible signs of quality on time and according to the SOPs			
Additional indicators		**Results**	
Reporting rate by physicians			
Reporting rate by pharmacists			
Reporting rate by nurses			
Reporting rate by other health professionals			
Reporting rate by patients			
Rate of non-serious ADR			
Rate of unknown ADR			
II. Activities of dissemination and promotion of the Pharmacovigilance system			
Dissemination and promotion of reporting of suspected adverse reactions in the geographic region that was designated			
Indicators	**Target**	**Results**	**Achievement**
7. N° of training courses conducted			
8. N° of promotional activities Eligible items: -Presentations in the context of pharmacovigilance, at conferences and other events -Involvement as trainers in classes of pharmacovigilance in pre- and post-graduation courses -Articles in the context of pharmacovigilance,			

published in scientific journals -Information brochures on pharmacovigilance			
Additional Indicators		**Results**	
Total n° of people participating in training courses			
Number of hours per training course (average)			
Number of people per training course (average)			
Number of trainees received in the RPU			
Number of studies proposed by the RPU to the CPS in the context of pharmacovigilance			
Number of Master's thesis being conducted under the supervision of the RPU			
Number of PhD's thesis being conducted under the supervision of the RPU			
Specific communication activities with INFARMED?			
Transmission of information about spontaneous reports to the CPS			
Activity		**Results**	
N° of spontaneous reports of ADR finalized in the database within the time limit			
N° of fatal or potentially fatal cases communicated to the CPS within 24h after its reception			
Total n° of fatal or potentially fatal cases received by the RPU			
N° of spontaneous reports introduced in the database with loading errors			
Indicators	**Targets**		**Achievements**
9. Rate of spontaneous reports introduced in the database within 7 days after its reception by the RPU			
10. Rate of urgent communications			
11. Rate of loading errors			

IV. Additional Activities
Indicators to be defined on a case by case basis, that must be described in the agreement / protocol specified for that purpose

Execution Rate