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THESIS

Pharmacovigilance:

Spontaneous Reporting Systems

HRADEC KRÁLOVÉ 2014 RNDr. Jindřich Srba

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I declare that this thesis is my original work of authorship. All literature and other sources which I used during the compilation of the work are listed in the bibliography and properly cited.

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CONTENT

1. Theoretical part

1.1. Pharmacovigilance

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. Furthermore, pharmacovigilance is also concerned with the safety of drugs in terms of clinical practice [1].

1.1.1. Milestones

The history of pharmacovigilance all around the world was constituted as a series of milestones that led to the introduction of re-evaluation of old concepts and brought new concepts within the discipline [2]. A few drug related safety issues accelerated the attitude of the concerned parties. These safety issues were related to a serious health disasters, where public health was threatened. Below are mentioned one of the most important cases, which influenced also an approach to the established practice.

- Elixir of sulphanilamide (1937)

  Fatal cases had occurred in the United States from the use of sulfanilamide in the form of elixir. Diethylene glycol, solvent used in elixir, had proved as a toxic agent, while dozens of people died [3]. The unfortunate experience led to a creation of the Federal Food, Drug and Cosmetic Act of 1938 [4].

- Thalidomide (1961)

  Incidence of phocomelia in European countries was associated to the use a thalidomide. The drug was initially tested in animals and then in humans, with result of extremely low toxicity in both animal and clinical testing [5]. However malforations in several

thousands of children concluded in a tragic story, with re-evaluation of an approach to systematic collection, evaluation and dissemination of information on adverse drug reaction (ADR) [6].

- Practolol (1975)

  Oculomucocutaneous syndrome developed in patients after the use of practolol [7]. Recording all adverse events experienced by patients and not just those regarded as ADRs to drugs might have revealed the ocular toxicity of practolol before the drug was marketed. This experience led to conclusion, that all events should be reported. [8].

- Cerivastatin (2001)

  In 1999 was reported for the first time of rhabdomyolysis in a patient taking a combination of cerivastatin and gemfibrozil [9]. Cerivastatin was withdrawn from the market in the United States and Europe in August 2001 and subsequently in Japan because of an increasing number of reports of rhabdomyolysis [10]. Since then, pressure to maintain independent advisory groups to conduct their own reviews and make recommendations was raised [11].

- Rofecoxib (2004)

  In September 2004 was withdrawn the drug from the market when, it became clear that it had serious cardiovascular side effects [12]. While the corresponding landmark trial, VIGOR, provided robust evidence for rofecoxib's gastrointestinal safety, it raised concerns about its cardiovascular toxicity, including a particularly worrying increase in the risk of myocardial infarction in 2000 [13]. However, a cumulative meta-analysis

performed published in 2004 concluded that rofecoxib should have been withdrawn several years earlier [14].

Emerging drug safety issues within 20th century accelerated a formation of international organizations, with their projects and programs, in order to set standards and ensure effective cooperation in the surveillance of the safety of medicinal products. The most important milestones related to the current European pharmacovigilance system, spontaneous reporting system (SRS) in particular, are described in Figure 1.1.1.

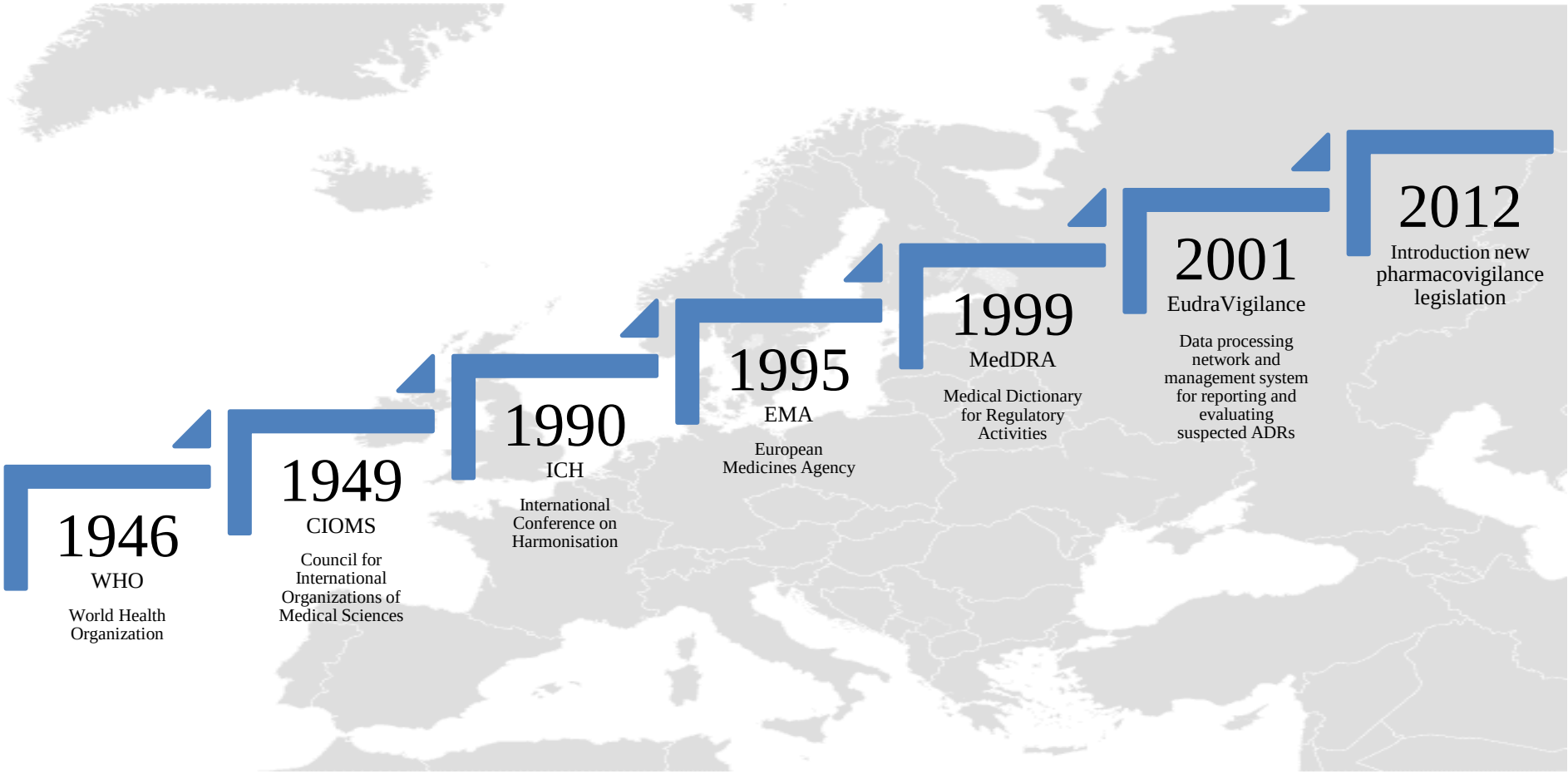

Figure 1.1.1 Major organizations, projects and programs with relevance to the current pharmacovigilance of adverse drug reactions in Europe.

1.1.1.1. World Health Organization

WHO acts as directing and coordinating authority for health within the United Nations system. In July 1946 delegates of 61 states signed the constitution of the World Health Organization (WHO). Later in 1948 a list of priorities was prepared. The list consisted of malaria, maternal and child health, tuberculosis, venereal disease, nutrition and environmental sanitation, public health administration, parasitic and virus diseases, and mental health. Programmes were developed in all these fields. Since then WHO is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends [15].

1.1.1.1.1. Council for International Organizations of Medical Sciences

WHO and UNESCO took the responsibility to establish an international, non-governmental, non-profit organization Council for International Organizations of Medical Sciences (CIOMS) in 1949. The main objectives of CIOMS is to facilitate and promote international activities in the field of biomedical sciences and to maintain collaborative relations with the United Nations and its specialized agencies. To achieve a broad range of drug safety topics, CIOMS has initiated programmes via working groups in order to develop consensus guidelines within areas such as international reporting of ADRs (CIOMS I reporting form), periodic drug safety update summaries and development safety update report, etc. [16].

1.1.1.2. International Conference on Harmonisation

The birth of International Conference on Harmonisation (ICH) took place at a meeting in April 1990, hosted by European Federation on Pharmaceutical Industries and Associations (EFPIA)

in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the United States met to discuss the wider implications and terms of reference of ICH.

At the first ICH Steering Committee meeting of ICH the Terms of Reference were agreed and it was decided that the topics selected for harmonisation would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorising new medicinal products [17].

1.1.1.2.1. Medical Dictionary for Regulatory Activities

In the late 1990s, the ICH developed MedDRA, a highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans. MedDRA was initially based on a terminology belonging to the Medicines and Healthcare products Regulatory Agency of the United Kingdom and was developed using the ICH process by the ICH partners, including WHO [18].

MedDRA is used for regulatory communication and evaluation of data pertaining to medicinal products for human use, among others post-marketing surveillance of medicinal products, e.g. ICH electronic communication within Individual Case Safety Report [19].

1.1.1.3. European Medicines Agency

The European Medicines Agency (EMA) is a decentralised agency of the European Union, located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. It began operating in 1995. From 1995 to 2004, EMA was known as European Agency for the Evaluation of Medicinal Products [20] and renamed to the EMA [21], it had the acronym EMEA until December 2009. Since then, a new acronym – EMA, started to be used.

The main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. One of the key regulatory activity maintained by EMA is safety monitoring of medicines. All suspected side effects that are reported by patients and HPs must be entered into EudraVigilance, the EU web-based information system that collects, manages and analyses reports of suspected side effects of medicines. These data are continuously monitored in order to identify any new safety information [22].

1.1.1.3.1. EudraVigilance

EudraVigilance is a data processing network and management system for reporting and evaluating suspected ADRs during the development, and following the marketing authorisation of medicinal products in the European Economic Area (EEA). The first operating version was launched in December 2001.

EudraVigilance supports among others the electronic exchange of suspected ADRs between EMA, National Competent Authorities (NCAs), MAHs, and sponsors of clinical trials in the EEA. EudraVigilance is also used for signal detection process, continual monitoring and evaluation of potential safety issues, and decision making process [23].

1.1.1.4. Current European pharmacovigilance legislation

Pharmacovigilance concept at EU legislation level was established in 1993 through a Council Directive (Council Directive 93/39/EEC amending Council Directive 75/319/EEC). Since then, a single Directive (2001/83/EC) in which pharmacovigilance is covered in Title IX (Articles 101–108) and Regulation (726/2004) in which pharmacovigilance is covered in Chapter 3 (Articles 21-29) were developed. Regulation and Directive have the objective to harmonise the national legislation of the EU Member States (MSs). Since July 2012 is being the EU

pharmacovigilance legislation amended (Directive 2010/84/EU and Directive 2012/26/EU; Regulation (EU) No. 1235/2010 and Regulation (EU) No 1027/2012).

1.1.1.4.1. Guideline on good pharmacovigilance practices

Practical measures to facilitate the performance of pharmacovigilance in accordance with the legislation through the guideline on good pharmacovigilance practices (GVP), which is being gradually implemented since July 2012. GVP apply to marketing authorisation holders (MAH), the EMA and national competent authorities in EU MSs. GVP is consisted of several modules covering a major pharmacovigilance processes. One of the first GVP, which came into effect, was Module VI – Management and reporting of adverse reactions to medicinal products, where are performed recommendations regarding the reporting of suspected ADRs [24].

1.1.1.4.2. Collection of reports

1.1.1.4.2.1. Solicited reports

Solicited reports of suspected ADRs are those derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, or information gathering on efficacy or patients compliance. For the purpose of safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they meet the criteria for expedited reporting [24].

1.1.1.4.2.2. Unsolicited reports

Unsolicited reports are reports from other sources like spontaneous reports, literature reports, or reports from other sources (e.g. media) [24].

1.1.1.4.2.2.1. Spontaneous reports

A spontaneous report is an unsolicited communication by a healthcare professional, patient or consumer to a competent authority, marketing authorisation holder or other organisation that describes one or more suspected ADRs in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection schemes [24].

Guideline on good pharmacovigilance practice (Module IV) published by EMA increase the importance of patients in the existing context of spontaneous reporting ADRs, which should be handled as spontaneous reports (directly submitted by patient or consumer) irrespective of any subsequent “medical confirmation”.

For better understanding of “medical confirmation” process we need to know the difference between ´adverse event´ and ´adverse drug reaction´, whose are defined in International Conference on Harmonization guideline E2D – Post approval Safety data management: Definitions and standards for expedited reporting:

- ´Adverse event´ is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.
- ´Adverse drug reaction´ concerns noxious and unintended responses to a medicinal product.

A ´reaction´, in contrast to an ´event´, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected.

For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an ADR [25].

1.2. Spontaneous reporting system in Europe

Pharmacovigilance concept, including SRS, at EU legislation level was established in 1993, however SRSs already existed in most countries which were MSs in 1993 and also in many of those joining the EU through the enlargement process in 2004. Some examples of the earliest established regulatory authorities in European countries are mentioned below.

1.2.1. The Netherlands

The Dutch Medicines Evaluation Board, was founded in 1963. Within the Netherland the MEB receives information from several sources: the Netherlands pharmacovigilance foundation Lareb; National Health Inspectorate and Marketing Authorization Holders (MAHs). Lareb (founded in 1991) is responsible for the processing and analysis of spontaneous ADR-reports received from HPs, pharmacists, MAHs and patients. In 2003, the Netherlands became one of the first countries in the world to allow patients to report adverse events [26].

1.2.2. The United Kingdom

The United Kingdom's spontaneous reporting Scheme was introduced in 1964, when all doctors and dentists in the United Kingdom were announced the launch of the new Yellow Card Scheme. Since then, pharmacists (1990s), nurses (2002), and patients (2008) were invited to submit any suspected ADRs they experience or are informed about [27].

1.2.3. Sweden

In Sweden, each HP entitled to prescribe drugs is obliged to report ADR to any of the six regional pharmacovigilance centres. Nurses, physicians and pharmacists employed by Medical Products Agency, established in 1965, handle these reports at the regional ADR centres affiliated to the departments of Clinical Pharmacology. Additional check-ups are performed by the MPA. These reports are continuously added to a database, which includes both all reported ADRs and information about current or withdrawn marketing authorisation in Sweden [28].

1.3. Source of spontaneous reports

Spontaneous reporting of ADRs was initially designed for HPs, dentists, other HPs (e.g. nurses) and pharmacists. Marketing authorisation holders shall record all suspected ADRs in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals (HPs), or occurring in the context of a post-authorisation study (Directive 2001/83/EC). Finally, direct submission of adverse events by patients/consumers were gradually included in the SRSs throughout respective NCAs established in European countries. Amended European pharmacovigilance legislation (Directive 2010/84/EC, Article 102 and 107).

1.3.1. Definition of direct patient reporting

For the purpose of this work, it is important to clearly define adverse event, which is directly submitted by patient or consumer to NCA. The most appropriate definition seemed to be the one used by PROSPER Consortium - ´Patient Reported Outcome of Adverse Event´ (PRO-AE) [29]. ´Patient Reported Outcome´ has already been established by EMA and Food and Drug Administration as any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s) [30, 31].

PRO-AE respects the definition of ´adverse event´, nevertheless for regulatory purpose should be handled as ´adverse drug reaction´. PRO-AE used in this thesis should be seen in the same way as ´adverse drug reaction´ submitted by HP.

1.3.1.1. Different attitudes to PRO-AE

The validity of a PRO-AE is being investigated since there was intention to include patients as reporters, who should be able to send their adverse event directly to NCA.

Patients have been allowed to report potential ADRs directly to the Medicines and Healthcare products Regulatory Agency (MHRA), via the Yellow Card Scheme since 2005 in the United Kingdom. In 2008, MHRA distributed questionnaires to determine patient views and experiences of making a Yellow Card report. Based on 1362 questionnaires sent to a research group was concluded easy to use of the current methods of reporting suspected ADRs by the majority of patients. On the other hand, respondents thought that awareness of direct patient reporting among HPs was low, with some HPs actively discouraging patients from reporting [32].

In 2010 was also performed a survey of British community pharmacists' views and practices concerning direct patient reporting of ADRs. Despite a low response rate (297 out of 1096), the study suggests that community pharmacists are not promoting direct patient reporting, in general. Furthermore, there was a view among some pharmacists that patients are unable to identify ADRs and should not be permitted to report themselves [33].

On the other hand PRO-AE may provide a positive complementary contribution to that of HPs by identifying different ADRs not identified from HPs reports alone [34].

1.3.1.2. PRO-AE and signal detection

Signal information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [35].

Potential pharmacovigilance impact of patient reporting was investigated in 2013, when data were analysed from all reports submitted directly to the Yellow Card Scheme between October 2005 and September 2007 in the United Kingdom. As a result, patient reporting provided a positive complementary contribution to that of HPs, however combination of reports from patients and HPs, resulted in the loss of some information [36].

2. Aims

Given the different nature of the patients, as reporters of ADRs, compared to HPs, should complications occur in the SRS maintained by competent regulatory authorities at local levels when these systems are required to include PRO-AEs.

The aim of this work was to evaluate position and potential complications related to the processing of PRO-AEs in SRSs established in European countries.

In this thesis were solved the following sub-tasks:

I. Characterization of reporting activity within SRSs established in European countries.

II. Evaluation of patients, in comparison to HPs, as subjects able to directly submit ADR reports.

III. Overview of the processing of PRO-AEs.

3. Practical part

3.1. Part I – Characterization spontaneous reporting systems within EEA

3.1.1. Introduction

Safety data are limited on a new medicine at the time marketing authorization has been obtained. Clinical trials performed up to the date of authorization are relatively restricted in terms of the target population (age, tender and ethnicity), associated co-morbidity or co-medication and conditions of use, as well as relatively short duration of exposure. The pharmacovigilance system is responsible for continuous drug safety evaluation after-market authorization. This is facilitated by several phases, such as data collection and management, signal detection, safety-issue assessment and decision-making [24, 37].

High-quality data and the interpretation thereof should improve the safe prescribing and rational use of medicine. At the beginning of this process data should be collected through literature searches, case-series studies, pharmacoepidemiology, clinical studies and the SRS. The latter is currently considered to be the most effective tool to collect ADR reports [38]. The SRS was established to collect post-approval safety information that would lead to the early detection of new or rare ADRs [39].

Not only do European countries have their own national safety databases, but two international databases are also maintained to manage ADRs. First, there is the EudraVigilance (European Union Drug Regulating Authorities Pharmacovigilance), with its safety database for electronic exchange of ADRs between the EMA, national competent authorities (NCAs), marketing authorization holders (MAHs) and sponsors of interventional clinical trials and non-interventional studies in Europe [40].

Secondly, there is the Uppsala Monitoring Centre in Sweden, which is responsible for the worldwide gathering of all serious ADRs received by regulatory authorities and companies. The robustness of the resources is definitely the main advantage safety databases [41]. Nevertheless, the SRS has been criticized for its weaknesses (see Fig. 3.1.1) [42, 43-47]. Previous findings relating to under-reporting revealed the main causes of these weaknesses to be lack of time, education and financial compensation, fear of revealing medication error and a generally negative attitude towards reporting activity.

3.1.2. Objective

In this part, we have attempted to evaluate the SRS and reporting activity among European countries. The main strategies used by NCAs to increase reporting in light of the above-mentioned problems were also assessed.

3.1.3. Methods

Data were gathered from two sources, namely, questionnaires and annual reports, and the sources compared. Spearman correlation coefficients were used to evaluate the reliability of measures in terms of reporting activity, and the Fisher exact test was used for analysis of the statistical significance of different conditions for reporting in European countries. Finally, an analysis of the strategy to increase reporting among countries was provided.

3.1.3.1. Data collection

The main subjects discussed in a standardized questionnaire in English were:

- Duties of HPs and MAHs,
- Distribution and management of safety information used by the NCAs,
- Encouragement of HPs and the public,

- Direct patient reporting,
- Total number of reports received per year.

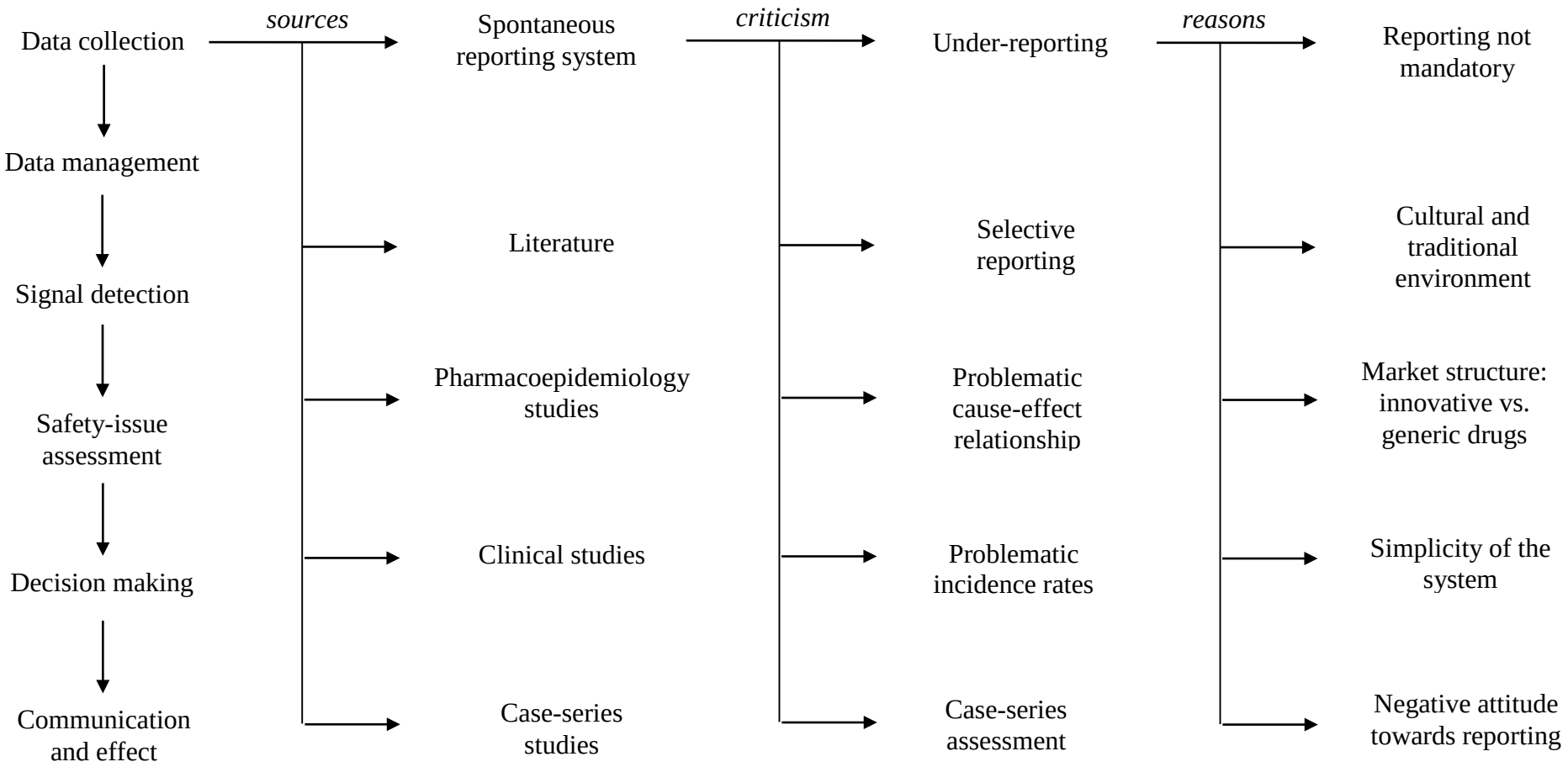

Fig. 3.1.1 Summary of the pharmacovigilance system, with main phases and criticism focused on under-reporting [38,42].

The questionnaires were sent to the pharmacovigilance departments of 30 NCAs. The survey was carried out between October and December 2010. In November 2010, the questionnaires were translated into the local national language and sent again directly to NCAs and their pharmacovigilance departments with no previous response. The second source was the annual report of each NCA, which is freely accessible on the respective official website.

3.1.3.2. Reporting ratio

The reporting ratio was defined as the total number of ADR reports in a safety database of a NCA per year related to population size, density of physicians or expenditure on health. The reliability of the reporting ratio was evaluated based on Spearman correlation coefficient analysis of various external criteria, namely, population size, density of physicians, doctors' consultations, total/public expenditure on health and total expenditure on pharmaceuticals [48, 49]. The data used were for 2007.

3.1.3.3. Population based reporting ratio

Population based reporting ratio (PBRR) is defined as the total number of ADR reports collected in a safety database of a NCA per year per million inhabitants (RYM): $PBRR01_{06} \times (R/N)$, where R is the number of ADR reports received by the NCA per year and N is the size of the population. Based on international long-term data and experience, a value of more than 300 RYM is considered to be reliable for signal detection [50]. European countries were divided into the following groups: (1) PBRR>300 RYM; (2) PBRR<300 RYM.

3.1.4. Results

3.1.4.1. Collection and validation of data

The SRS of 26 of the 30 European countries was evaluated. Four countries were excluded from the analysis due to a lack of data. Twenty questionnaire based responses were checked against the data in by annual reports that were available for 15 countries. An additional six annual reports of countries with no questionnaire-based response were included in the analysis. Data from questionnaires and annual reports were compared in 15 countries with 80% identical data (n=12).

3.1.4.2. Reporting ratio

To evaluate the reliability of the PBRR, we calculated Spearman correlation coefficients for total expenditure on health (ρ=0.499, p=0,023, n=21), public expenditure on health (ρ=0.477, p=0.035, n = 20), total expenditure on pharmaceuticals (ρ=0.435, p=0.057, n=20), density of physicians (ρ=0.242, p=0.290, n=21) and doctors' consultations (ρ=−0.181, p=0.472, n=18). None of the correlation coefficients for the variables related to physicians or expenditure-based reporting ratios with the external criteria were significant on the 5% level. As Fig. 3.1.2 shows, total expenditure on health is the best correlation for reporting ratios based on population size (ρ=0.499, p=0.023, n=21), expenditures on pharmaceuticals (ρ=0.365, p=0.114, n=20) and density of physicians (ρ=0.336, p=0.136, n=21). Only PBRR was significant on the 5% level. The values of Spearman correlation coefficients suggest that a weak link may exist between reporting ratios and the density of physicians or doctors' consultations.

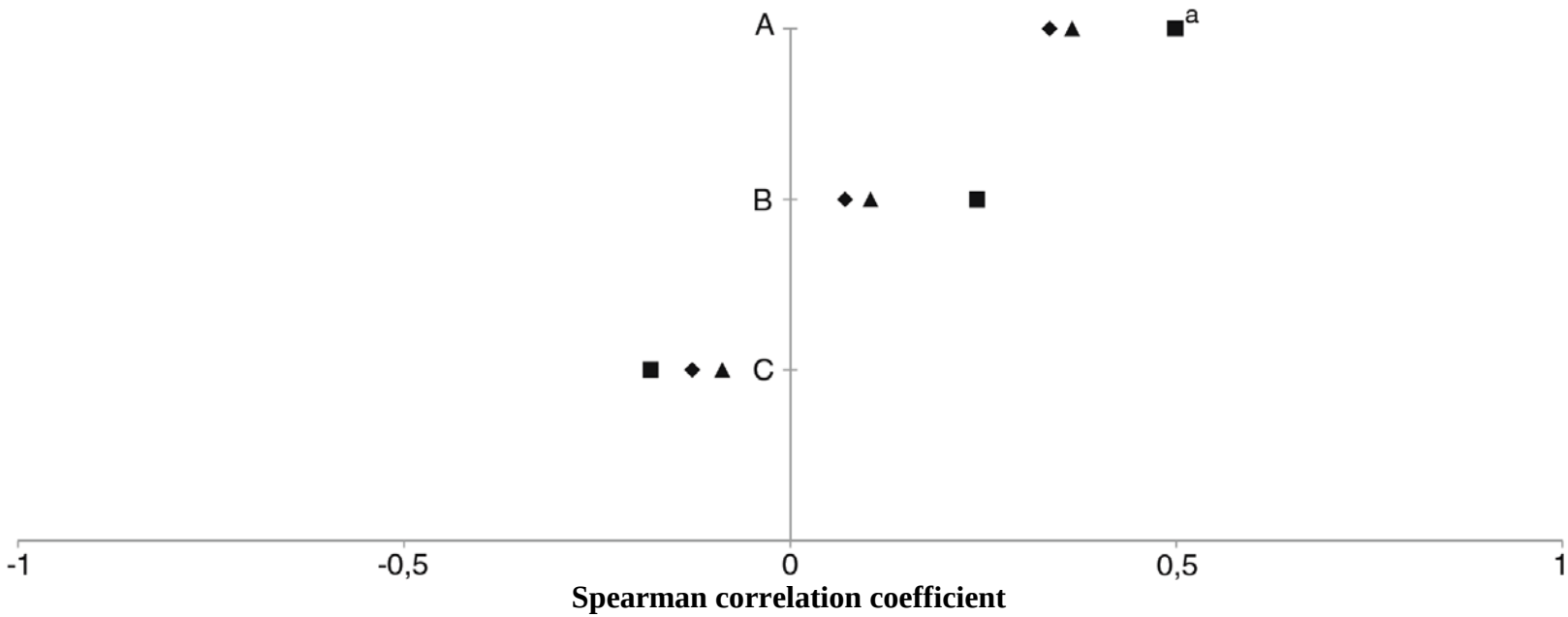

Fig. 3.1.2 Reporting ratios in relation to external criteria in 2007. Spearman correlation coefficients were calculated to account for unsymmetrical distributions. *X-axis: -1* Strong negative correlation, *0* no correlation, *1* strong positive correlation. *Symbols* represent number of total adverse drug reaction reports per million inhabitants (*square*), per expenditures on pharmaceuticals per inhabitant (*triangle*) and per density of physician per 10,000 inhabitants (*diamond*). *Y-axis* represents external criteria: *A* Total expenditures on health, *B* density of physicians per 10,000 inhabitants, *C* doctors´ consultations per inhabitant. *Superscript a* Correlation was significant at the 5% level.

3.1.4.3. Reporting activity

The average number of recorded ADR reports per year in the period 2007–2009 was 201,042 in EudraVigilance [51] and with 119,097 in the analyzed countries. The reporting ratio values per year are shown in Table 3.1.1.

The average PBRR in the period 2007–2009 was 400 and 243 based on the safety databases of EudraVigilance and NCAs, respectively. The PBRR values per year of the study period are shown in Table 3.1.2.

Evaluation of the PBRR revealed large differences between the countries analyzed (see Fig. 3.1.3). However, the effect of the increased PBRR in 2009 in comparison with that of recent years was found in almost all countries. This trend is even more striking in countries with a PBRR of>300, such as Denmark, Sweden, Ireland, Iceland, Norway, the Netherlands, Malta, the UK Kingdom, France, Austria, Belgium and Spain. Increasing reporting activity was also found in countries with a PBRR of<300.

3.1.4.4. National SRS

The PBRR value for 2009 was used to categorize the countries analyzed into two groups—one consisting of the 12 countries with a PBRR of>300 RYM, and the second consisting of the 14 countries with a PBRR of<300 RYM (see Table 3.1.3). In each of the countries evaluated (n=26), MAHs have a legal obligation to report serious ADRs; however, such reporting is more or less voluntary for HPs; in only 69% of the countries are HPs legally obliged to report serious ADRs. The legal obligation for HPs to report serious ADRs is more prevalent in countries with a PBRR of>300 RYM than in those with a PBRR of<300 RYM (50 vs. 79%, two-tailed p00.22, Fisher’s exact test).

Table 3.1.1 Population size and number of ADRs in the EEA and MS.

Year	Population [52]		Number of ADR reports	
	EEA	MS	EudraVigilance [51]	MS
2007	500,315,899	488,330,307	155,834	101,465
2008	502,771,258	490,732,848	227,927	115,873
2009	504,854,440	492,761,574	219,367	139,954

ADRs – Adverse Drug Reactions; EEA – European Economic Area; EudraVigilance – European Union Drug Regulating Authorities Pharmacovigilance; MS – Member States of the EEA except Cyprus, Greece and Liechtenstein.
Data from Cyprus, Greece and Liechtenstein are not included in the analysis.

Table 3.1.2 Population Based Reporting Ratio.

Year	PBRR	
	EudraVigilance (RYM)	MS (RYM)
2007	500,315,899	488,330,307
2008	502,771,258	490,732,848
2009	504,854,440	492,761,574

PBRR – Population Based Reporting Ratio; RYM – total number of reports per million inhabitants per year; PBRR=106 x (R/N), where R = number of ADR reports received by NCA and N = population.

Patients are also allowed to report suspected ADRs directly to NCAs in 69% of the countries, with this right more prevalent in countries with a PBRR of>300 RYM than in those with a PBRR of<300 RYM (75 vs. 64%; two-tailed p00.68, Fisher's exact test). Finally, regional centres had been established in 42% of the countries. More countries with a PBRR of>300 RYM had established regional centres to support pharmacovigilance activity than those with a PBRR of <300 RYM (67 vs. 21%, two-tailed p00.04, Fisher's exact test).

A more detailed analysis of actions related to the SRS was possible using data contained in the annual reports of countries with a PBRR of >300 RYM [53-64]. A summary of the key attributes of the SRS were determined to be:

- Effective communication [53, 55-58, 62], including follow-up questions to physicians, encouraging "Direct Healthcare Professional Communications", media stimulation, informative campaigns;
- Public and media attention [53-57], including attention-attracting public health topics such as vaccination;
- Education [55, 62], including under-graduate and postgraduate training, improvement of inter-field cooperation and information exchange;
- Simplicity [53, 59], such as flexible and uncomplicated reporting, electronic reporting forms.

3.1.5. Discussion

Comparison of the total numbers of ADR reports, based on questionnaires and the annual reports of 15 countries, revealed differences in three cases. In one case, the numbers differed slightly and in two cases the questionnaire-based numbers were rounded. In these three cases, we gave preference to data based on annual reports as the officially published source.

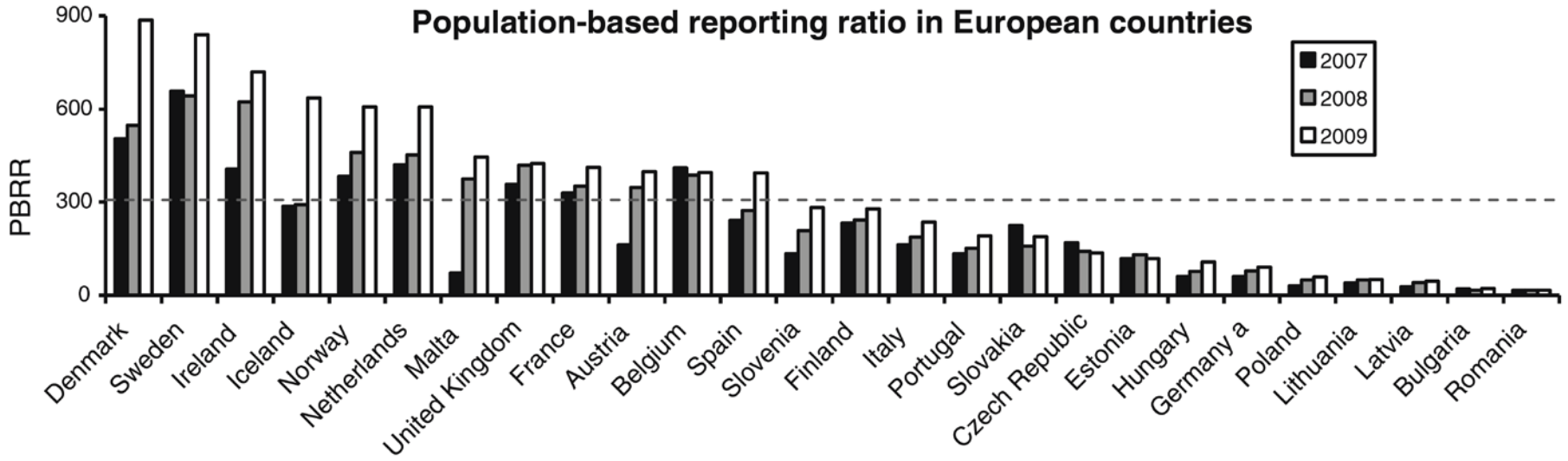

Fig. 3.1.3 The population based reporting ratio (PBRR) in European countries. *Broken line* PBRR=300. A PBRR of>300 for any one country is considered to be potentially robust to detect rare and very rare adverse events. Data from Cyprus, Greece and Liechtenstein are missing. Spontaneous reports in Luxemburg are submitted to one of the French regional center. *EEA* European Economic Area. The *´a´ following Germany* indicates that only reports from the Paul-Ehrlich Institute were included in the analysis (and not from BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte).

Table 3.1.3 Strategies and requirements of national competent authorities in terms of spontaneous reporting systems and PBRR.

Member state (year of establishing national pharmacovigilance centre [65])	Healthcare professionals	Patients	Regional centre	PBRR in 2009 (rym)
	Obligation to report serious ADRs	Possibility to report ADRs		
Denmark (1968)	Y	Y	N	886
Sweden (1965)	N	Y	Y	840
Ireland (1969)	N	Y	Y	719
Iceland	N	Y	Y	626
Norway	Y	Y	Y	607
Netherlands (1963)	N	Y	Y	606
Malta (2004)	N	Y	N	445
United Kingdom 1964)	N	Y	Y	425
France (1973)	Y	N	Y	412
Austria (1979)	Y	N	N	398
Belgium (1976)	Y	Y	N	395
Spain (1983)	Y	N	Y	394
Slovenia (1983)	Y	Y	N	282
Finland (1966)	M	N	N	279
Italy (1980)	Y	Y	Y	236
Portugal (1992)	Y	N	Y	192
Slovakia (1986)	Y	Y	N	189
Czech Republic (1986)	Y	Y	N	137
Estonia (1994)	Y	N	N	119
Hungary (1985)	Y	Y	N	108
Germany (1978)	N[a]	Y	N	91[b]
Poland (1972)	Y	Y	Y	59
Lithuania (1999)	Y	N	N	51
Latvia (2001)	Y	Y	N	46
Bulgaria (1974)	Y	N	N	22
Romania	N	Y	N	17

Y, yes; N, no; rym, reports per million inhabitants per year

This table is divided into two parts according to PBRR in 2009: first 12 countries listed in column 1, 2009 PBRR>300 rym, 14 countries under the division, 2009 PBRR<300 rym Data from Cyprus, Greece and Liechtenstein are not included in the analysis. Spontaneous reports in Luxemburg are submitted to one of the French regional center.

[a] In Germany the reporting of adverse events following vaccination is mandatory by law

[b] Only reports from Paul-Ehrlich Institute were included (not from BfArM - Bundesinstitut für Arzneimittel und Medizinprodukte)

3.1.5.1. Limitations

A number of limitations to the study reported here need to be considered. Firstly, the study could be limited by the lack of data available for certain countries. The average PBRR calculated for the 26 European countries considered in our analysis was lower than the average PBRR based on the EudraVigilance safety database. Nevertheless, these four excluded countries would have to have an average PBRR of more than 4,500 RYM to reach EudraVigilance level. This is not probable, considering the highest PBRR value of these countries was 886 RYM (Denmark). Secondly, several types of reporters are used to define the source. Unfortunately, our analysis of the annual reports revealed that either the type of reporter was not identified at all or reporters were categorized into almost 13 types [55]. A homogenous description of reporters would be beneficial as it is known that a PBRR of up to 300 RYM should be based on at least 30% of the serious ADRs originating from more than 10% of HPs [50].

In addition to the known reporting biases [66], there is always a risk of duplication. Data quality and their validation are crucial to reduce duplicates [67-69]. Consequently, the PBRR should be perceived as the highest value.

3.1.5.2. Spontaneous reporting systems

Based on the correlation with external criteria, we perceive the PBRR to be the most reliable measure. Despite the small sample size, the PBRR had the highest correlation to expenditures on health and public expenditure on health, with significance at the 5% level. However, this result should be interpreted with caution due to other factors with a potential to influence reporting activity. Further investigation would be beneficial.

Under-reporting as the main weakness is affected by many factors [37, 38, 42], but not by the obligation of HPs to report ADRs. The PBRR was not negatively influenced by the voluntary reporting of HPs in Iceland, Ireland, the Netherlands, Sweden or the United Kingdom. The same is true for direct patient reporting, which did not prove to be statistically significant to increase reporting activity. Countries with regional centers are more likely to report ADRs. Regional centers ensure the fast and dynamic transition of important information in the field of pharmacovigilance. Several regional centers have already started under-graduate and postgraduate training for pharmacists associated with cooperative efforts and information exchange [55, 62, 70].

Our analysis of the annual reports of countries with high reporting activity revealed the main strategies used to support reporting, namely, encouragement and education of HPs and patients, public attention, and simplicity of reporting. These findings are consistent with those, which were related to reporting of communication importance between HPs and patients and active stimulation of HPs and patients by NCAs to report ADRs [71-73]. NCAs use follow-up responses [74] or an informative campaign related to actual health problems occurring in society. For example, a positive effect on reporting activity was observed in French non-university hospitals after regular visits by clinical research associates [75].

What else may affect reporting activity?

In general, a high reporting activity was observed in those Western European countries where regional centers were established mostly in the 1960s and 1970s (Table 3; [43]). Considerably more work will be needed to determine to what extent the type of health system or health culture may affect reporting activity.

3.1.6. Conclusion

Pharmacovigilance in Europe is composed of many regulations, directives and guidelines [76, 77]. These rules generate standards for pharmacovigilance practice that are implemented into national legislation. This study provides a survey of SRSs maintained by NCAs to collect ADR reports.

The results of this study reveal that the PBRR is the most reliable measure of reporting activity. In 2009, almost half of the countries evaluated in our study reached the value PBRR significant for signal detection. The increase of reporting activity at the national level correlates with that at the international level, indicating a vital transmission of ADR reports from NCAs to EudraVigilance. In general, therefore, it seems that the attitude of NCAs is essential for any enhancement of reporting activity, even at the international level.

We also found a positive effect of regional centers on reporting activity; in contrast, the legal obligation of HPs to report ADRs did not have a positive effect on reporting activity. Reporting activity is generally supported by education and encouragement of HPs, which is in agreement with previous findings.

Taken together, these results support the strong recommendation of close cooperation with reporters of ADRs at the local level (regional centers, NCAs) to maintain the increasing reporting activity. Further research is needed to determine the effectiveness of data collection and the use of these data for signal detection.

3.2. Part II – Evaluation of the position of ADR reports submitted by patients

3.2.1. Introduction

Since July 2012, ADR report directly submitted by patient to NCAs should be always accepted based on the new European legislation Regulation (EU) No. 1235/2010 and Directive 2010/84/EU [76, 77]. The European Commission reviewed the system and proposed new EU pharmacovigilance legislation, in order to continue to improve patient safety. The legislation was the biggest change to the regulation of human medicines in the European Union since 1995. One of the key aspects of implementation the new European legislation is to take account of, and encourage, the growing involvement of patients in the reporting of ADRs. In fact, this process began since 2003. ADR reports directly submitted by patients started in Denmark and the Netherlands since 2003, in the United Kingdom since 2005, in Sweden since 2008, or in Norway since 2010. On the other hand, there were countries not actively collecting patient reports like Finland, France, Germany, Ireland, Portugal or Spain [78-81].

Decision to include patients as additional source of directly submitted ADR reports was based on a few articles concerned with this topic. An investigation performed in 1999 confirmed HPs as the main source for reports of serious and unknown ADRs in hospitalized patients, yet patients seemed to report more ADRs to new drugs [82]. Another study performed in 2002 suggested that patients do not report all of the symptoms that they suspect to be ADRs to their general practitioner and that the general practitioners do not record all of the symptoms [83]. This practice contributes to the under-reporting, which is considered the main weakness of the current system [43]. Hence, patients as additional sources of reports are increasingly perceived to be important contributors to the SRS [85].

3.2.2. Objective

The main objective of this part was to characterize the position ADR reports directly submitted by patients in European countries before the introduction of the obligation to accept these reports from July 2012.

3.2.3. Methods

3.2.3.1. Questionnaire-based analysis

Analysis was done by survey using a self-administered structured questionnaire. Questionnaires were distributed on February 2011 to the general e-mail address of NCAs established in 30 different European countries (EEA member countries in 2011). Addressed subjects were asked for their response on March 2011. To increase the response rate, a second encouragement was conducted at the end of March 2011. In case of no response, email address of related pharmacovigilance department at NCA was used at the beginning of April 2011. Final questionnaire collection was concluded in April 2011.

The questionnaire consisted of two parts, qualitative and quantitative. For the first part, questions were related to the processing of ADR reports from patients. For the second part, the total numbers of ADR reports from patients in comparison with those from HPs from 2007 until 2010 were requested. The content of questionnaire was validated by the employee of pharmacovigilance department at State Institute for Drug Control in the Czech Republic. Validation was based on the evaluation of the relevance of the requested data and their availability at NCAs. Questionnaires were prepared in English language.

3.2.3.2. Literature search

A review was conducted in compliance with the PRISMA statement [86]. Studies related to the comparison of ADR reports submitted by patients and HPs were considered for inclusion. The search strategy was based on the electronic databases MEDLINE (Ovid) and EMBASE (Ovid). The search terms included: patients, consumers, HPs, physicians, ADRs, report, reporting, spontaneous, pharmacovigilance and surveillance. Text search terms and controlled vocabulary search terms for MEDLINE (MeSH) and EMBASE (EMTREE) were used. The searches covered the period from 1 Jan 2003 to 31 Dec 2011, inclusive. The search itself was performed on 23 May 2012. The decision to include an article was made primarily based on the title and abstract. Duplicate articles were detected and removed manually. In case of doubt, the full article was obtained for the final classification decision. Full-text articles were obtained for all of the selected articles.

3.2.3.3. Inclusion criteria

Articles published from 2003 to 2011 were included with the subject of the establishment of accepting ADR reports submitted by patients directly to NCAs. Articles published prior to 2003 were not included, because at that time any of the European countries actively supported the collection of ADR submitted by patients. To meet the inclusion criteria, the articles had to be prospective or retrospective studies, which investigated ADR reports submitted by HPs and patients to NCAs established in the European MSs. Detected articles should compare one of the following criteria: reporter age and gender, most frequently reported ADRs and/or drugs, and the seriousness of the ADRs.

3.2.3.4. Exclusion criteria

Articles based solely on the analysis of reports from HPs or patients were excluded, to achieve the most uniform data dedicated to the comparison of reports from both sources. Reviews or meta-analyses were not included, as the main objective was to provide an overview of the studies concerned with the direct comparison of ADR reports from HPs and patients. Case reports and case series were also excluded.

3.2.3.5. Citation searching

The reference list of each included study was checked to identify further relevant research studies. The full paper was obtained for each study being considered for inclusion in this review.

3.2.4. Results

3.2.4.1. Processing of ADR reports

17 out of 30 NCAs sent back the questionnaires (response rate 57%). In 12 countries, patients were allowed to report suspected ADRs by letter, telephone or via the internet. In 10 countries, ADR reports submitted directly by patients did not need to be medically confirmed and were directly accepted. Also in 10 countries, ADR reports submitted directly by patients were used for signal detection. In 6 countries, reports were directly accepted and used for signal detection at the same time: Denmark, Ireland, the Netherlands, Norway, Sweden and the United Kingdom (Table 3.2.1).

Table 3.2.1 Processing of adverse drug reaction reports from patients at the national level.

Group of ADR reports from patients	I Direct acceptance for safety signal generation						II Medically confirmed				III Not used for signal detection		IV Not accepted				
Responses based on questionnaires send from NCAs	Denmark	Ireland	Netherlands	Norway	Sweden	United Kingdom	Czech Republic	Estonia	Germany	Slovenia	Hungary	Latvia	Austria	Finland	Lithuania	Malta	Portugal
Patients are allowed to send reports	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N
Reports used for signal detection	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N					
Reports are medically confirmed	N	N	N	N	N	N	Y	Y	Y	Y	N	N					

European countries were divided into groups of adverse drug reaction reports from patients based on acceptability and use for signal detection. NCA – National Competent Authorities; N – No; Y – Yes.

3.2.4.2. Reporting ratio

Reporting ratio describes the ratio of ADR reports from patients to the total number of ADR reports submitted to NCAs. Considerable variation of the reporting ratio exists across national systems per year (Fig. 3.2.1). This variation was observed not only across different European countries, but also on a year-by-year basis. The contribution of ADR reports from patients to the total number of reports was 3% in Ireland, 7% in Norway, 8% in the United Kingdom, 16% in Sweden, 17% in the Netherlands, and 24% in Denmark during the period 2007–2010.

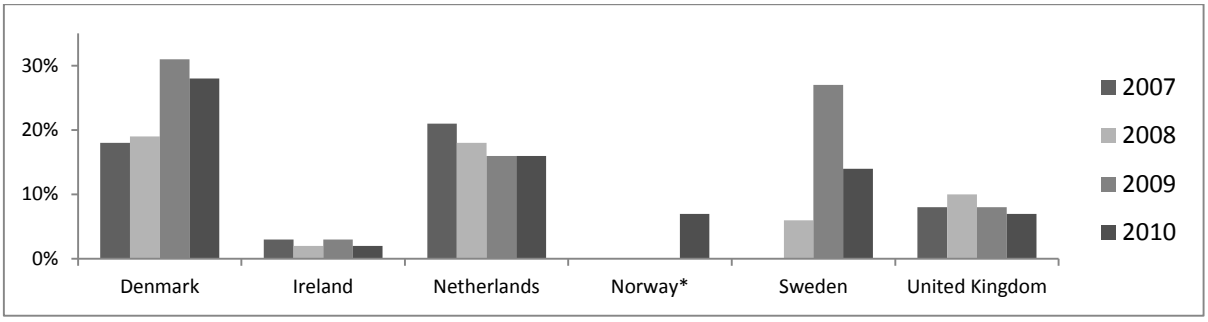

Fig. 3.2.1 Reporting ratio of adverse drug reaction (ADR) reports from patients to the total number of ADR reports in the six member states of the European Economic Area, where reports from patients are directly accepted and used for signal detection. Data are based on questionnaires received from 17 NCAs. *Collection of ADR reports from patients began only since 1 Mar 2010.

3.2.4.3. Literature review

A literature search produced a limited number of abstracts, very few of which were relevant. 4 articles included the assessment of ADR reports from patients and HPs in those European countries where ADR reports directly submitted by patients have been accepted (see Fig. 3.2.2). Two were from the Netherlands, one was from Denmark and one was from the United Kingdom.

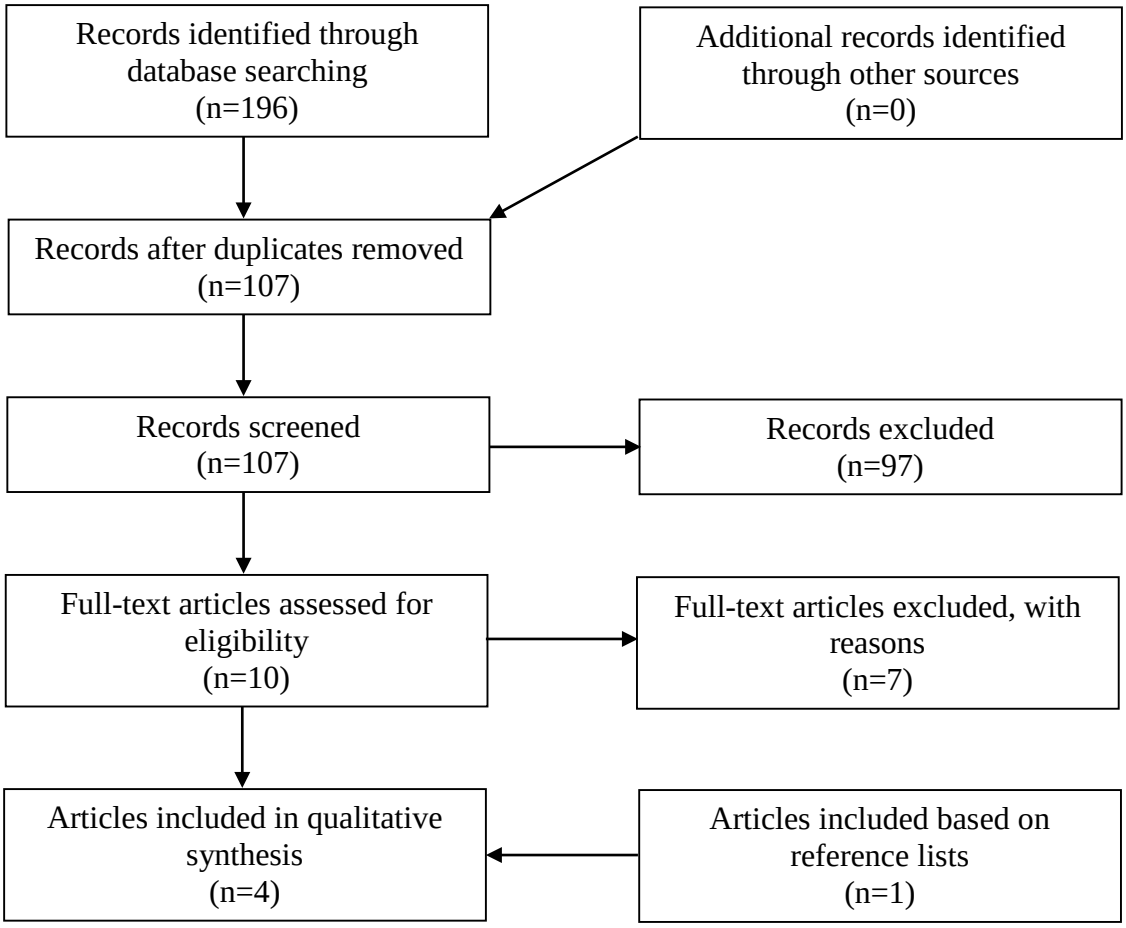

Fig. 3.2.2 Flow diagram of selection of studies. Structure derived from PRISMA [84, 86].

3.2.4.4. General findings

The summary of the comparison of characteristics of the reporters, ADRs, and drugs, based on selected articles, is shown in Table 3.2.2. We were interested to see if the characteristics of reporters (HPs vs. patients) were evaluated by the authors of selected articles as similar or different.

3.2.4.4.1. The Netherlands

In 2008, were analyzed reports from HPs (consisting of general practitioners, specialist doctors and pharmacists) and patients received by the Netherlands Pharmacovigilance Centre between

April 2004 and April 2007. Patients submitted 2 522 reports concerning 5 401 ADRs. HPs submitted 10 635 reports concerning 16 722 ADRs. This means that each patient report contained, on average, 2.1 ADRs, whereas HPs' reports had 1.6 ADRs. Regarding the reports, the mean age of patients (48 years) was similar to HPs (49 years). Also, 63% of the female patients were comparable to 61% from HPs. Statins were the most frequently reported drugs for patients and HPs. Moreover, the top five drugs showed great similarity. Also, similarity between reports from patients and HPs concerning the System Organ Class was observed. Finally, the seriousness of the reports was not significantly different from patients (19.5%) and HPs (21%) [87]. Comparison of the 3-year period resulted in the acknowledgement of no differences in terms of age, gender, the most frequently reported ADRs and drugs, and the percentage of serious ADRs in general between patients and HPs.

Another study was performed in the Netherlands by 2009. Patients submitted 265 reports, concerning 780 ADRs, about statins to the Dutch safety database from March 2007 to August 2007. HPs submitted 111 reports involving 172 ADRs about statins in the same period. This means that each patient report contained, on average, 3.0 ADRs per patient report, in comparison to 1.5 ADRs per HP report. Patients who reported ADRs were younger (57.3 years) than HPs (61.9 years). Of the patient reports, 64% were male in comparison to 52% of HPs. An overlap exists in the top 10 of the most frequently reported ADRs, however patients reported more in musculoskeletal disorders and psychiatric disorders. No substantial differences were observed in the percentage of reported seriousness among patients (15.1%) and HPs (11.7%); which was the only similar characteristic of ADR reports submitted by patients and HPs [88].

Table 3.2.2 Article outcomes.

FIRST AUTHOR, PUBLICATION YEAR	COUNTRY	COVERED PERIOD	NUMBER OF REPORTS (HP/PATIENTS)	NUMBER OF ADVERSE DRUG REACTIONS (HP/PATIENTS)	COMPARISON OF REPORTERS – PATIENTS AND HEALTHCARE PROFESSIONALS				
					AGE	GENDER	MOST FREQUENTLY REPORTED		SERIOUSNESS
							DRUGS	ADRS	
de Langen J, 2008	the Netherlands	April 2004 – April 2007	10 635 / 2 522	16 722 / 5 401	similar	similar	similar	similar	similar
van Hunsel F, 2009	the Netherlands	March 2007 – August 2007	111 / 265	172 / 780	different	different	not evaluated	different	similar
Aagaard L, 2009	Denmark	January 2004 – December 2006	5 775[a] / 544	13 831[a] / 1700	not evaluated	not evaluated	different	different	different
McLernon DJ, 2010	the United Kingdom	October 2005 – September 2007	20 949 / 5 180	44 429 / 20 358	similar	similar	different	different	different

Comparison of reporters – patients and healthcare professionals (HP). Varying results were detected among respective articles (columns) and characteristics (lines) of each article except for that from de Langen (the first line), where all characteristics of the patients as direct reporters were similar to those of HPs. a) Numbers of reports and adverse drug reactions were based physicians, pharmacists, other HPs and lawyers.

3.2.4.4.2. Denmark

In Denmark were analyzed 6 319 ADR reports related to 15 531 ADRs extracted from the Danish safety database for the period 2004 to 2006. Patients submitted 544 ADR reports corresponding to 1 700 individual ADRs. The rest of 5 775 ADR reports, which were submitted by physicians, pharmacists, other HPs and lawyers included 13 831 ADRs. Each patient report contained, on average, 3.1 ADRs, whereas other source of reports had 2.4 ADRs. Age and gender of the reports was not analyzed in the article. There was a significant difference in the distribution of ADRs by type of reporter and System Organ Class or type of drug. Additionally, 46% of the ADRs reported by patients were classified as serious in comparison to 76% from physicians, pharmacists and other HPs. Comparison of the 2-year period resulted in the acknowledgement of differences in terms the most frequently reported ADRs and drugs, and the percentage of serious ADRs in general between patients and other reporters including HPs, other HPs and lawyers [89].

3.2.4.4.3. The United Kingdom

A total of 26 129 reports from the Medicines and Healthcare products Regulatory Agency were analysed in the United Kingdom by 2010, which were received from October 2005 to September 2007. Of these, 5 180 were patient reports and 20 949 were HPs. Patients reported 20 358 ADRs (3.9 ADRs per report) whereas HPs reported 44 429 ADRs (2.1 ADRs per report). The median age of reporters was similar for patients (54 years) and HPs (53 years). Also gender representation was similar to patient reports (62.7% females) and HPs (57%). Reporting forms for patients were slightly different as the patients were not asked the seriousness of the ADR but only the severity of the reaction. Seriousness is characterized by consequences of ADR (e.g. death, hospitalization). Assessment of severity is largely subjective. Reactions can be

described as mild, moderate, severe, or lethal in the patient report. Therefore Medicines and Healthcare products Regulatory Agency of the United Kingdom evaluated the seriousness of the reaction based directly on the report by the patient. 55.5% of HPs considered reports as serious in comparison to 44.8% patients' declaration that suspected ADR was bad enough to affect everyday activities. More patient reports mentioned a nervous system problem (41.5%), however the most common System Organ Class for HPs was skin and subcutaneous tissue (23.2%). Also differences were detected in terms of suspected drugs. A comparison of patients' and HPs' ADRs resulted in the acknowledgement of differences in the seriousness and the most frequently reported drugs and ADRs [72].

3.2.4.5. Strengths and limitations of the study

This study covers the European countries to outline the comparison of position ADR reports submitted by patients. The major strength was the collaboration with the 17 NCAs, which enabled to us to obtain a general overview of position and processing ADRs in 2011. However, questions concerned to requirements for validation ADR reports or characteristic of method of reporting ADR reactions would require more in-depth analysis to better understand the real impact of patients ADR reports in the national safety database. It would be advantageous to understand the formal validation process of reports and the number of excluded reports. To compare characteristics of reports submitted by patients and HPs was reviewed a literature related to ADR reports in countries, where ADR reports submitted by patients were already accepted.

3.2.4.6. Risk of bias

3.2.4.6.1. Selection bias

The selection bias of the literature search could be considered as very low. It was not a coincidence that the articles detected by the search used data from the national databases of the Netherlands, Denmark and the United Kingdom, as their national pharmacovigilance systems are of very high level compared with the other European countries.

3.2.4.6.2. Selective reporting bias

Selective reporting bias in the three out of four articles was assessed as having a low risk, as there were included all ADR reports included in the national safety database. In the Dutch study performed by 2009 were ADR reports investigated selectively related to statin use after media attention. Therefore, the reporting might be influenced by information presented in media. Patients submitted 265 reports concerning 780 ADRs. HPs submitted 111 reports involving 172 ADRs about statins in the same period. This means that each patient report contained, on average, three ADRs, whereas HPs' reports had 1.5 ADRs. The total number of ADR reports in this period was 833 for patients and 1609 for health professionals [88].

3.2.4.6.3. Outcome data bias

ADR reports investigated in the selected articles were extracted from national safety databases. These reports were previously processed and filtered for the purposes of each particular study. It would be beneficial to work with all initial ADR reports submitted by HPs and patients that were not yet processed and included in the national safety databases. For example, in the study performed in Denmark was mentioned as limitation of the study that there were investigated

consumer reports from Danish ADR database and not the original reports. Therefore validity of ADR reports could not be evaluated [89]. Also, one of the limitations in one of the study performed by 2010 was incompleteness of the certain the fields in the patient reports so there was a large proportion of missing data [72].

3.2.5. Discussion

The national pharmacovigilance systems in the 17 European countries, whose responses to questionnaires were received in this study, were established in the years from 1963 to 2004. This broad time span indicates to the diversity of the respective systems. ADR reports from HPs were mandatory in most of the countries (11 vs. 5; data for Norway were not available). ADRs were generally collected only by national centres; in six cases, regional centres and/or major hospitals were also used to support the collection of ADR reports. Pharmacovigilance activities and outcomes are highly dependent on the cultural traditions and attitudes of doctors. In the comparison of any pharmacovigilance data across European countries, we should always keep in mind the variable history of national pharmacovigilance systems and their development, despite the coordination of pharmacovigilance procedures and applications by the EMA since 1993.

3.2.5.1. Processing ADR reports from patients

This is the first summary review to present the different attitudes of NCAs to ADR reports from patients. The majority of NCAs declared the acceptance of ADR reports directly from patients. Nevertheless, variations existed in the further processing of these reports.

NCAs in Hungary and Latvia declared that they did not use ADR reports from patients for signal detection by 2011. Reports collected from patients cannot therefore influence any safety

issue related to the use of the drugs in these countries. The reason for the collection of ADRs directly from patients could be to support and cooperate with patients regarding pharmacovigilance activities. Nevertheless, in case of acceptance ADR reports submitted by patients, attention should be focused to the utilization of these reports for signal detection.

In several countries, ADR reports are medically confirmed prior to their inclusion in a safety database, as stated by NCAs in the Czech Republic, Estonia, Germany and Slovenia. Therefore, the number of patient reports is reduced by the unknown quantity of those excluded during the assessment procedure. Additionally, a more detailed exploration of the effectiveness and administrative burden of medical confirmation should be undertaken.

In several countries (Denmark, the Netherlands and the United Kingdom), ADR reports from patients are accepted without any medical confirmation and are used in safety databases for signal detection. The only control that is possibly provided by NCAs is a formal evaluation (for completeness of the report); however, this cannot be stated for certain, as it was not part of the questionnaire analysis.

As can be seen, there is a disparity in the processing of ADR reports from patients. Different attitudes about the collection and use of ADR reports from patients pointed to the problematic position of direct reporting by patients across European countries. The question how this will be changed with the implementation of new European legislation since July 2012 directing that ADR reports from patients should always be collected [76, 77].

3.2.5.2. Reporting ratio

Various reporting ratios of ADR reports from patients to the total number of reported ADRs could be observed among different countries. Moreover, various reporting ratios were observed throughout the years in some of the countries. It should be kept in mind that collecting ADR reports from patients has only recently started and its position is currently being formulated in established national pharmacovigilance systems. General factors like legal framework conditions, technical resources, collaboration with stakeholders, and general quality management may influence the submission ADR reports directly by patients [37].

3.2.5.3. Comparison of ADR reports

Varying outcomes were detected across the analyzed articles that compared ADR reports from HPs and patients in terms of age and gender of reporters, most frequently in reported ADRs and drugs and in the seriousness of reports. A systematic review of comparative studies revealed both differences and similarities between reporter types [90]. As a limitation of our study, it should be acknowledged that the studies analyzed did not clearly describe the assessment process of ADR reports when they are first received by NCAs. It can be assumed that all reports were probably already controlled on the basis of data quality, and that some of them could also be medically confirmed prior to incorporation into the safety database. To enhance the validity of the data that were compared, studies should always describe the similarities and differences in the processing of reports after ADR collection.

3.2.6. Conclusion

Spontaneous ADR reporting by patients has become a valuable pharmacovigilance tool and has already contributed to safety signal generation [45, 80]. At this moment, ADR reports directly submitted by patients are becoming more or less an integral part of national pharmacovigilance

systems as an additional source of reports for the generation of safety signals. The comparison of ADR report processing from patients and from HPs revealed differences in terms of acceptance of ADR reports from patients, their medical confirmation, and their inclusion in the safety database, which is necessary for signal generation. Moreover, various outcomes were observed across studies that compared characteristics of reporters, drugs, and ADRs between HPs and patients.

This study revealed the need for analysis of the effective use of ADR reports from patients in the national pharmacovigilance systems, particularly in the processing of ADR reports from patients from the time they are collected by NCAs.

3.3. Part III – Overview of the processing of PRO-AE

3.3.1. Introduction

ADRs represent a major public health problem and are estimated to account for 28% of all emergency department visits [91], up to 6.5% of all hospital admissions [92], and 6.4% of hospital fatalities [93]. All sources of information for detecting ADRs (e.g., clinical trials, observational studies, patient registries or SRS) have limitations, resulting in ADRs being undetected, unsubstantiated or underreported [94]. While spontaneous reporting by HPs is a very important approach, direct patient reporting could represent a major source of adverse event reporting [73, 80, 83, 85, 95-98].

Reports directly submitted by patients became of high importance for EMA, which resulted in the establishment of the new pharmacovigilance legislation. Since July 2012 EU MSs should collect and record direct patient reporting. Reporting of suspected ADRs by patients/consumers to NCAs is promoted and facilitated through Guidelines on Good Pharmacovigilance Practices. In accordance with Articles 101(1) and 107a(1) of Directive 2001/83/EC, each MS shall have in place a system for the collection and recording of all reports of suspected ADRs that occur in its territory and which are brought to its attention by patients or consumers. ADR is defined as a response to a medicinal product which is noxious and unintended. This includes ADRs which arise from use of a medicinal product within or outside the terms of the marketing authorization, including overdose, misuse, abuse, medication errors and occupational exposure [24].

For the purposes of this study, Patient Reported Outcomes of Adverse Events (PRO-AE) was used, according to definition presented in the recent study, where PRO-AE is defined as any untoward medical occurrence, whether or not considered treatment- or intervention-related, that

is reported directly by the patient without interpretation by a clinician or anyone else. PRO-AEs may be collected by both structured and unstructured reports [29].

3.3.2. Objective

A few comparative studies of patients and HPs as reporters of ADRs have already been undertaken to review similarities and differences between reporter behaviors [72, 87-89, 90]. A review of the methods used in ADRs was performed in 2010 in a survey of 11 countries, including five in Europe [81]. To our knowledge, no study was performed to evaluate the processing of PRO-AEs prior to the establishment of new European pharmacovigilance legislation [76, 77]. The present study was conducted to obtain an overview of the processing of PRO-AE by NCA in different European countries.

3.3.3. Methods

3.3.3.1. Step 1 – Questionnaire Development

Development of the questionnaire consisted of three phases: i) definition of study dimensions; ii) formulation of objectives; and iii) characterization of respondents.

Study dimensions were detected on the basis of amended Regulation No. 726/2004 and amended Directive 2001/83/EU and Guideline on good pharmacovigilance practices - Module VI, where is clearly described management and reporting of ADRs to medicinal products. Critical issues (dimensions and objectives, Table 3.3.1) were detected on the basis of general principles in relation to the collection, recording and reporting of suspected ADRs associated with a medicinal product, which are applicable to NCAs, as mentioned in section ´Structures and Processes´ of the Guideline [24].

As we were interested in European countries, where pharmacovigilance activities are overseen by EMA, the survey was sent to NCAs in the 30 countries of the EU and EEA that are responsible for overseeing use of human medicines. Contact details to NCAs were obtained from the EMA [99].

Table 3.3.1 Dimensions of knowledge on ADR reporting and their objectives.

Dimension	**Objective**
Source of ADR reports	Distribution of subjects (with the focus on patients) that are allowed to report ADRs to NCAs.
Reporting tools	Distribution of methods used for reporting PRO-AEs.
Structures and processes	Knowledge of validation and acceptance of PRO-AEs.
Time management	Approximate estimation of the time required for the processing of PRO-AEs.
Proportion of reported PRO-AEs	Proportion of submitted PRO-AEs in relation to the all submitted ADRs.

ADR - Adverse drug reaction; NCA - National Competent Authorities; PRO-AE - Patient Reporting Outcomes of Adverse Event.

3.3.3.2. Step 2 – Questionnaire Validation

Questionnaire validation consisted of three phases: i) evaluation by reliable experts; ii) reliability of the assessment; and iii) revision of questions.

The initial questionnaire was submitted by e-mail to academics with expertise of NCAs, who evaluated the appropriateness, relevance and formulation of each question. Each question was discussed for its reliability with respect to the main study objective. Fourteen of the initial 30 questions were excluded: five based on the low correlation and nine based on the high probability of difficulties in obtaining the required data. Additionally, four of the remaining 16 questions were modified and four completely new questions were added. The final questionnaire contained 20 questions. The first 10 questions (Table 3.3.2) were related to

activities of NCAs from January 2012 to June 2012, prior to changes in European pharmacovigilance legislation. The other 10 questions were identical to the first 10 questions except they were under the new legal framework, which was introduced in June 2012.

Table 3.3.2 Main items used for compilation of the final version of the questionnaire.

	Items included in the final version of the questionnaire
1	Distribution of reporters of ADR reports submitted to NCAs.
2	Possibility of patients to directly submit potential ADRs to NCAs.
3	Reporting tools used by HPs to submit ADR reports.
4	Reporting tools used by patients to submit ADR reports.
5	Inclusion of ADR reports directly submitted by patients into national safety databases.
6	Validation used by NCAs.
7	Amount of excluded ADR reports directly submitted by patients measured in ranges (e.g. up to 25%).
8	Reason for exclusion of ADR reports directly submitted by patients.
9	Time spent processing ADR reports directly submitted by patients.
10	Proportion of ADR reports submitted directly by patients in comparison to the total amount of submitted ADR reports.

ADR – Adverse Drug Reaction; HP - Healthcare Professional; NCA – National Competent Authority.

3.3.3.3. Step 3 – Questionnaire Distribution

The survey was sent by e-mail to the NCAs of all 30 European countries. The questionnaire was in English, validated for its content, and was sent out in February 2013 and then 1 month later to non-respondents increase the response rate. After 2 months, the questionnaire was sent out one final time by e-mail directly to pharmacovigilance departments of NCAs of those

countries that had not responded. To allow respondents to obtain clarification on any of the questions, the questionnaire included contact details of the corresponding authors.

3.3.4. Results

Of the 30 distributed questionnaires, e-mail responses were obtained from NCAs of 18 countries, and 15 (50%) attached a completed questionnaire. With one exception, additional explanation of the questionnaire was not required by any of the respondents, suggesting that the questionnaire was not hard to understand. On the other hand, we do not know the clear reason why questionnaires from other 15 NCAs were not completed and sent back.

3.3.4.1. Reporting tools

NCAs were asked to define the number of ADR reports submitted by specific reporting tools used by patients and by HPs for the second half of 2012. Four reporting tools were used by NCAs: a paper form, e-mail, a web form and telephone. No other method was mentioned in the questionnaire. Eleven out of 15 NCAs specified the reporting tools used by patients and HPs. A web form was used in most cases. In three countries were all PRO-AEs submitted by web form. On the other hand, web forms were not used for PRO-AE reporting in the other three countries.

3.3.4.2. Validation

All suspect ADR reports should be validated by NCAs. Formal validation is based on assurance that the minimum information is included, which a technical parameter that could be performed by anybody, with no special requirement of qualification [24]. Formal validation was performed

by all responding NCAs who could also comment on the causal relationship between the suspected medicinal product(s) and the suspected ADR.

A causal relationship based on validation by expert judgment (with or without medical validation) [100] or by algorithms [101] was presented in the questionnaire as medical validation. Seven out of 15 NCAs stated that medical validation was performed in relation to PRO-AEs reported in the second half of 2012 (Table 3.3.3).

3.3.4.3. Exclusion of PRO-AEs

Formal and/or medical validation was requested to prevent acceptance of those PRO-AEs that were irrelevant or had incomplete data. NCAs were asked to determine the approximate number of excluded ADR reports from patients and the reason for exclusion. NCAs of nine countries found no valid reason for exclusion of any PRO-AEs. Five countries excluded a small number (less than 25%) of PRO-AEs. In this group, four out of five NCAs stated the main reason for exclusion was deficiencies in information. The remaining NCA did not disclose any reason for exclusion. The majority (up to 75%) of PRO-AEs were excluded in Estonia, where the NCA declared medical deficiencies as the main reason for exclusion.

Table 3.3.3 Description of methods of reporting ADRs and validation process performed by National Competent Authorities.

Country	Reporting tool used for submitting ADRs by Patients / Healthcare Professionals (%)				Validation process	
	Paper	E-mail	Web form	Telephone	Formal validation	Medical validation
Bulgaria	0/60	0/6	100/34	0/0	Yes	Yes
Czech Republic	36/36	64/64	0/0	0/0	Yes	Yes
Denmark	No data available				Yes	**No**
Estonia	5/10	0/0	90/90	0/0	Yes	Yes
Iceland	0/5	10/5	90/90	0/0	Yes	Yes
Ireland	No data available				Yes	Yes
Latvia	0/10	0/90	100/0	0/0	Yes	Yes
Lithuania	25/50	0/50	0/0	75/0	Yes	**No**
Malta	NA/10	NA/90	NA/0	NA/0	Yes	**No**
Netherlands	0/5	0/0	100/95	0/0	Yes	**No**
Norway	0/100	0/0	100/0	0/0	Yes	**No**
Portugal	No data available				Yes	**No**
Slovenia	5/50	5/50	90/0	0/0	Yes	Yes
Sweden	5/8	5/2	90/90	0/0	Yes	**No**
United Kingdom	16/33	81/67	0/0	3/0	Yes	**No**

Zero value could mean that the reporting tool was not established or it was established, but not used by reporters. ADR – Adverse Drug Reaction; NA - Not applicable; NCA – National Competent Authority.

3.3.4.4. Recording of PRO-AEs in the safety database

PRO-AEs have been required to be collected and recorded by each MS of the EU since July 2012. NCAs were asked to state their recording of PRO-AEs in a safety database, and their use for signal generation as for ADR reports from HPs or MAHs. In the first half of 2012, PRO-AEs recorded in the safety database were used for signal generation in seven out of 15 European countries. In five of the 15 European countries, PRO-AEs were recorded but not used for signal generation. The remaining three NCAs did not specify their answer. In the second half of 2012, PRO-AEs recorded in the safety database were used for signal generation in 13 out of 15 European countries. In one country PRO-AEs were recorded but not used for signal generation. The remaining NCA did not provide an answer.

3.3.4.5. Time-relatedness

A general overview of the proportion of submitted PRO-AEs in all ADR reports, and the time devoted to the management of PRO-AEs, is described in Table 3.3.4. Data were based on responses from 12 out of 15 NCAs. Responses from the remaining three NCAs did not provide complete data. In seven out of 15 (64%) countries, PRO-AEs accounted for up to 5% of ADRs. A higher PRO-AE rate was observed in Norway (6%), the United Kingdom (7%), Estonia (10%), Sweden (16%) and the Netherlands (35%). Time spent on management of PRO-AEs in relation to other pharmacovigilance activities was specified by responding countries as up to 5% in six cases and up to 25% also in six cases. There were interesting differences between countries. In Bulgaria, the Czech Republic and Slovenia, PRO-AEs accounted for only 2% of all submitted ADR reports but these accounted for 5–25% of ADR management time. On the other hand, in Estonia and Norway, PRO-AEs accounted for 10% and 6%, respectively, of ADR reports, but only 5% of the management time.

3.3.5. Discussion

3.3.5.1. Patient Reported Outcome of Adverse Event

Reporting of ADRs was initially mainly related to the reporting by HPs, who are considered as professionals with medical background allowing to evaluate the causality of the adverse event and the use of medicinal product. In case of direct reporting adverse events by patients, more comprehensive definition should be used to clearly differentiate the (in)ability of patients to understand and establish causal relationship between adverse event and the use of medicinal product. PRO-AE definition presented in the recent study was considered as the most appropriate in the context of the current study [29].

3.3.5.2. Reporting tool

The majority of PRO-AEs were reported by web forms. Such forms can be open-ended or checklist-based. Open-ended questionnaires can effectively provide important information on how a drug may affect the patient using it and influence his or her personal life [102]. Checklist-based web forms are more sensitive in identifying potential ADRs. However, this type of questionnaire may lack specificity in respect to detection of an ADR [103]. Therefore, a generic patient-reported ADR questionnaire, which was feasible and reliable for reporting any ADR, has been developed [104]. On the other hand, the level of sophistication of web forms varies considerably. Moreover, web forms require access to the internet, which may be commonplace in many countries, but not in others. In 2012, access to the internet in households of six European countries was less than 60%. Internet connection of countries, where web forms were not used for PRO-AE reporting, was 63% in the Czech Republic, 61% in Lithuania and 86% in

the United Kingdom [105]. Therefore, alternative methods such as paper forms or telephone had to be used to ensure full accessibility.

Table 3.3.4 Management of PRO-AEs.

Country	Proportion of PRO-AE	Approximate time spent on PRO-AE
Bulgaria	2%	5–25%
Czech Republic	2%	5–25%
Estonia	10%	<5%
Iceland	5%	<5%
Latvia	2%	<5%
Lithuania	1%	<5%
Portugal	1%	<5%
Netherlands	35%	5–25%
Norway	6%	<5%
Slovenia	2%	5–25%
Sweden	16%	5–25%
United Kingdom	7%	5–25%

Countries with data on the proportion of PRO-AEs in comparison with all submitted ADR reports and approximate time spent on management of PRO-AEs. PRO-AE – Patient Reported Outcome of Adverse Event.

3.3.5.3. Validation of ADR reports

All reports of suspected ADRs should be validated before reporting them to the relevant authorities to ensure that the minimum information is included in the reports. This process is termed formal validation. At least four criteria should be met to consider an ADR report as valid. These include an identifiable reporter, an identifiable patient, at least one suspected substance/medicinal product, and at least one suspected ADR. The lack of any of these four elements means that the case is considered incomplete and does not qualify for inclusion in a safety database.

In general, forms for reporting ADRs lack questions to assess causality and questions about the nature of the ADR, such as its seriousness, severity, frequency, and time course, which are relevant in the medical evaluation of the ADR [106, 107]. A robust database of ADR reports, which can be used for signal generation, should be filled with valid data to avoid misinterpretation and false signal generation. Medical validation was performed by half of the national regulatory authorities. However, neither the method nor the nature of medical validation was specified in the questionnaire. In further research would be interesting to investigate the process of medical validation more thoroughly.

3.3.5.4. Reporter validation

There could always be a risk of bias where the reporter and his/her ADR was not validated or confirmed. A case of a suspect ADR report submitted by a patient cannot be downgraded to a report of a non-related ADR even if the contacted HP (nominated by the patient for follow-up information) disagrees with the patient's suspicion, as is stated in the Guideline on Good Pharmacovigilance Practice, Module VI. Therefore, PRO-AE could always increase the possibility of false reports. From this point of view, reporter validation is of great importance.

3.3.5.5. New approach brings new challenges

Since 2012, when new pharmacovigilance legislation was introduced, all countries in the EU have been required to collect PRO-AEs. The main intentions were to promote collaboration with the public, to increase the final number of submitted ADR reports [78], and to reduce the burden for the pharmaceutical industry and regulators [108]. To evaluate these goals will require more time; however several changes were detected after introduction of the new legislation. Our study indicated that there was an increase in utilization of PRO-AEs in safety database and for signal detection. There are five countries that use PRO-AEs in relation to the period before the implementation of the new legislation. This could be considered as very positive, especially for the patients themselves, as it increases the impact of cooperation with them.

Since a patient is a different type of reporter compared with HPs or MAHs, the validation process is crucial. There is a specific procedure for formal validation; however, no clear requirement for medical validation of PRO-AEs has yet been established. Additionally, we should also deal with the issue of intentionally false PRO-AEs. Therefore, several tasks should be considered in the future:

- Is it necessary to validate PRO-AEs by HPs or other competent persons, or not?
- Should causality assessment of a PRO-AE prevent always be provided?
- How can submission of a false PRO-AE be prevented?

3.3.5.6. Time management

After validation of the processes to ensure data of the highest quality, the next step is to determine how much time their management consumes. To our knowledge, no study has determined the proportion of time devoted to the management of PRO-AEs in relation to the

total number of submitted ADR reports. Despite the relative inevitable imprecision of time estimates, our study showed that the time attributed to management of PRO-AEs did not necessarily correlate with the proportion of reports. For a better understanding, it would be beneficial to determine the number of employees involved in pharmacovigilance activities, the performed pharmacovigilance activities, and whether and to what extent external staffs were involved. Further study is therefore necessary.

3.3.6. Conclusion

Each EU MS (under representation by NCAs) should have in place a system for the collection and recording of all reports of suspected ADRs, which are brought to its attention by HPs, patients or MAHs. Based on the results of this study, the process of collection and validation of PRO-AEs proved to be variable among countries. Although the new legislative amendments introduced numerous measures that should decrease the administrative burden for the pharmaceutical industry and regulators, accepting and managing PRO-AEs could mean an increase in the procedural burden. A few critical processes, such as medical validation, reporter validation and time management, remain to be examined to ensure the quality of processing PRO-AEs. Nevertheless, implementation new legislative requirement regarding collection and processing PRO-AEs positively supported the involvement of patients in surveillance of drug safety.

4. Summary of results

4.1. Characterization of SRSs within European countries

- PBRR was determined as the most reliable measure of reporting activity for the purpose of characterization spontaneous reporting activity among European countries.
- In 2009, almost half of the European countries reached the value PBRR significant for signal detection.
- Throughout the years 2007 to 2009 was found positive correlation of reporting activity at national and international level in terms of total amount of ADRs in respective safety databases.
- Legal obligation of HPs to report ADRs did not correlate with increase of reporting activity.

4.2. Evaluation of the position of ADR reports directly submitted by patients

- ADR reports directly submitted by patients are becoming more or less an integral part of national pharmacovigilance systems in European countries.
- The comparison of processing ADR by NCAs, which were submitted by patients and HPs revealed differences in terms of acceptance, medical confirmation process, and inclusion in safety database.
- Various outcomes were observed across studies that compared characteristics of reporters, drugs, and ADRs between ADR reports submitted by patients or HPs as reporters.

4.3. Overview of the processing of PRO-AE

The process of collection ADR reports and validation of PRO-AEs proved to be variable among European countries.

Critical processes, such as medical validation and reporter validation should be of high interest to ensure the quality of processing PRO-AEs.

5. Commentary

5.1. Questionnaire-based analysis

The aim of the study was to investigate the SRSs in respective MS of EEA, which are maintained by NCAs. Questionnaire based analyses were pre-dominantly used to survey basic information and practice performed by NCAs.

There are variety of ways to achieve desired answers to any number of questions. The methods should be reliable to include qualitative and quantitative approaches. Specifically, considered methodologies were face-to-face interviews, telephone interviews, written questionnaires or internet questionnaires.

With regard to the distance of the individual NCAs from each other, it was only logical to choose internet as distribution channel for questionnaire based analysis. The advantages of online survey are (i) the access to groups or organizations, who would be difficult to reach; (ii) saving time; (iii) and saving costs [109]. The crucial question was to choose the right form of questionnaire distribution.

Internet questionnaire seemed to be a good choice, however this procedure represented a great risk of low-interest of subjects (responsible personnel at NCAs) to go/open an internet link with questionnaire(s), as there are a lot of spams at users' emails. A solution could be a preliminary communication with respective subjects, but potential language barrier represented considerable complications for the course questionnaire based analysis itself.

Questionnaires distributed directly to the email addresses of NCAs was considered as the most reliable approach to receive enough completed questionnaires back. Nevertheless, attainment of the relevant respondent within each NCA, clear identification of person/respondent and potential language barrier and represented some complications.

5.1.1. Interviewed subjects

So as to obtain as many answers as possible, distribution strategy of the questionnaire with cover letter in English was based primarily on the contacts given by EMA [99]. In case of no response, reminder was sent to the interviewed subjects. In no response was obtained, an email address directly to pharmacovigilance department of relevant NCA was searched and used for distribution the same questionnaire. Finally, those NCAs with no response was sent for the last time questionnaire in English with cover letter written in the local language.

5.1.2. Missing data

Some of the data from those NCAs with no response after all the email attempts were obtained directly from websites of NCAs with annual reports presented for the relevant year(s).

5.2. Quantity of PRO-AE

Based on the survey of 50 countries worldwide performed in 2014, most of them have implemented PRO-AE into their SRSs. It seems that an online reporting form increases the rate of reporting. Nevertheless, to increase the number of reports, each country should promote NCA-initiated ADRs reporting systems [110].

EMA in the context of pharmacovigilance works with the fact that patients are also capable to report suspected ADRs to medicinal products. It is therefore appropriate to facilitate the reporting of suspected ADRs to medicinal products by both HPs and patients, and to make methods for such reporting available to them. MSs facilitate patient reporting through the provision of alternative reporting formats [76, 77].

5.2.1. New approaches to capture PRO-AE

Some of the European countries have previously developed, next to paper form, e-mail and telephone, a web based systems to enable consumers to report post-approval suspected ADRs directly to the NCAs (e.g. Yellow Card scheme by MHRA in the UK) in an attempt to address underreporting by HPs. At the moment, web based questionnaires became the main tool for collection ADR. Nevertheless, there is increasing discussion and attempts to use social media and application for hand devices (e.g. tablets, mobile phones) to capture additional amount of ADRs directly from patients [29, 111].

5.2.2. Promotion of PRO-AE

5.2.2.1. Legislative approach

With the introduction of new pharmacovigilance legislation (Directive 2010/84/EU) was also specified a way of promotion reporting ADRs directly by patients for all medicinal products, which is being gradually applied when any variation or renewal of medicinal product is submitted by MAH. In package leaflets should be included a standardized text, expressly asking patients to communicate any suspected ADRs to his/her doctor, pharmacist, HP or directly to the national SRS.

5.2.2.2. NCA approach

NCAs, in general, promote reporting of ADRs by the support of effective communication, public and media attention, education and increase the availability of simple tools for collecting ADR reactions. These tools were focused on all potential reporters of ADR, which were mainly considered HPs and MAHs in most of the European countries prior to 2012. It would be

interesting to overview tools, actions and degree of effort applied by NCAs, to inform public about the possibility to report ADR.

5.2.2.3. Unregulated area

In addition to those already established systems, there are other non-regulatory approaches to increase the success in capturing safety data based on social networks or specialized health social networks [112].

Specialized health social networks are primarily intended for the purposes of patient support and education rather than PRO-AE instruments. However, there could be found data related to the experience with ADRs. The potential to mine ADRs data from unstructured text presented in social networks would be feasible, but there is a need for further development before wider utilization [113].

5.3. Quality of PRO-AE

Despite many important advantages, quality of ADR reports captured through SRS is considered as low in comparison with other methods, like cohort event monitoring, or targeted spontaneous reporting [114]. PRO-AEs could brought a different view regarding ADR reporting, therefore it is considered as important issue to receive reports from both groups to assess the true nature of the ADR [115].

Effort to increase the quantity of captured ADR reports escalates already existing complications with quality of these reports like biases and duplications. Above that, a new qualitative complications arise since educational and professional background of HPs is completely different to the patients as reporters. Issues like medical relevance verification and source verification were not sufficiently discussed.

5.3.1. PRO-AE validity

In 2002 was performed a methodological study concerned to patient reporting of potential ADR. Patients were asked through the questionnaire to identify any symptoms experienced over the previous year due to the drug they used. Result of the study pointed to the willingness of patients to report symptoms of ADR [83].

Prior to establishment of direct patient reporting, comparison studies were performed in the Netherlands, United Kingdom or Denmark. Various outcomes were detected across the analyzed articles that compared ADR report from HPs and patients in terms of age and gender of reporters, most frequently reported ADRs and drugs and seriousness of reports (see Part II – Evaluation of the position of ADR reports submitted by patients). In general, there is recommendation to actively include patients/consumers in systematic drug surveillance systems, and their reports should be taken as seriously as reports from other sources.

Recently was assessed the validity of PRO-AE based on questionnaire with a 3-month or 4-week recall period. Patients were asked to report potential adverse event they experienced related to any drug in a daily diary for a 3-month period. Thereafter, they completed the questionnaire with either a 3-month or 4-week recall period. The validity was assessed by comparing daily diary and questionnaire. In conclusion, the validity of PRO-AE was considered as low [116].

5.3.2. Verifying medical relevance

The comparison of ADR report processing from patients and HPs revealed differences in terms of reported ADRs, frequency, seriousness, etc. Various outcomes and conclusions among published observational studies give no clear understanding of PRO-AEs medical relevance. In general, there are different types of reporters of potential ADRs with specific educational background:

- HPs (physicians, dentists, etc.) – medical education;
- Pharmacists – pharmaceutical education;
- MAHs – responsible person for pharmacovigilance should have medical, pharmaceutical, or at least scientific background of education;
- Patients – any kind of education.

Medical relevance of PRO-AE should not be overlooked, considering that all ADR reports should be transmitted from relevant national safety databases to a single safety database performed by EMA, called EudraVigilance, which is used for collection Individual Case Safety Reports and statistical signal detection [117].

5.3.3. Verifying sources of ADR reports

Because of the various natures of patient populations, a range of different tools for collection ADRs, analytical approaches and methodologies may need to be deployed to meet different PRO-AE requirements. A classification based on whether or not the relevant patient population is pre-specified (rather than just pre- or post-approval) provides a rational basis for further subdividing the safety populations [3].

For instance, the dataset is more structured and the patient population is better defined in post-approval, prespecified populations (e.g. phase 4 clinical trials and prospective observational studies) than in post-approval, non-prespecified patient populations. There is also distinction between clinical trials and safety surveillance systems that may have no clear denominator representing the total number of patients. Therefore, frequency cannot be established.

Additionally, the question of possibility to verify reporter of PRO-AE in the context of data protection is of high importance. Reporter should be always identifiable for several purposes, e.g. due to follow-up reports. Nevertheless data protection must not be violated, which is a

complication mainly for social media, which is considered as additional source of PRO-AEs. Finally, the issue false reporting was not raised and discussed, despite the fact that PRO-AEs are much more susceptible in comparison to reports from HPs or MAHs.

6. Final conclusion

SRS is the easiest to establish and the cheapest to run but was criticized for poor quality reports and underreporting. Results of this thesis demonstrated an increasing tendency in reporting activity, in general. Comparison of the PBRR revealed a positive trend in the total amount of collected ADR reports in respective European countries throughout the years. It is also quite reasonable to expect the trend will continue, due to public engagement in pharmacovigilance activities.

While quantity of ADR reports is being increased throughout the years, quality issues should not be overlooked. Due to different nature of patients and various outcomes of comparison patients and HPs, as ADR reporters; and various attitudes of NCAs, validity of PRO-AEs remains as an unsolved challenge in SRSs.

To complete the results following studies should be performed:

- Additional survey of the current attitude and management of PRO-AE by NCAs, since changes were performed, due to the ongoing implementation of the new pharmacovigilance legislation.
- To better to understand the needs and complications of potential reporters with no medical educational background.

Presented results have led to the following recommendations:

- Medical validation of PRO-AE should be clearly defined.
- Medical validation of PRO-AE should be always performed prior to inclusion to a safety database due to different nature of PRO-AE and ADR.
- Attitude of NCAs should be re-evaluated.

- Methodology for reporters' verification should be establish to increase the validity of PRO-AE.

7. References

(Vancouver style)

1 Arthur N, Bentsi-Enchill A, Couper MR, Duclos P, Edwards IR, Fushimi T, et al. *The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products*. The United Kingdom: IOS Press and Uppsala Monitoring Centre; 2002. http://apps.who.int/medicinedocs/en/d/Js4893e/ (accessed 26 August 2014).

2 Rägo L, Budiono S. Drug regulation: history, present and future. In: Van Boxtel CJ, Santoso B, Edwards IR (eds.) *Drug Benefits and Risks: International Textbook of Clinical Pharmacology*. 2nd edn. Sweden: IOS Press and Uppsala Monitoring Centre; 2008. pp. 65-77.

3 AGN. The elixir sulfanilamide-massengill. *Canadian Medical Association* 1937; 37(6): 590.

4 Wax PM. Elixirs, diluents, and the passage of the 1938 federal food, drug and cosmetic act. *Annals of Internal Medicine* 1995; 122(6): 456-461.

5 Ing GM, Olman CL, Oyd JR. Drug-Induced (Thalidomide) Malformations. *Canadian Medical Association Journal* 1962; 87(24): 1259-1262.

6 World Health Organization. WHA18.42 *Adverse drug reaction monitoring system*. World Health Organization. Report number: 6, 1965.

7 Wright P. Untoward effects associated with practolol administration: oculomucocutaneous syndrome. *British Medical Journal* 1975; 1(5958): 595-598.

8 Skegg DCG, Doll R. The case for recording events in clinical trials. *British Medical Journal* 1977; 2(6101): 1523-1524.

9 Pogson GW, Kindred LH, Carper BG. Rhabdomyolysis and renal failure associated with cerivastatin-gemfibrozil combination therapy. *The American Journal of Cardiology* 1999; 83(7): 1146.

10 Marwick C. Bayer is forced to release documents over withdrawal of cerivastatin. *British medical journal* 2003; 326(7388): 518.

11 Psaty BM, Furberg CD, Ray WA, Weiss NS. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. *The Journal of the American Medical Associaton* 2004; 292(21): 2622-2631.

12 Singh D. Merck withdraws arthritis drug worldwide. *British Medical Journal* 2004; 329(7470): 816.

13 Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *The New England Journal of Medicine* 2000; 343(21): 1520-1528.

14 Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; 364(9450): 2021-2029.

15 Charles J. Origins, history, and achievements of the world health organization. British medical journal 1968; 4(2): 293-296.

16 CIOMS. *About us. http://www.cioms.ch/index.php/about-us (accessed 06 September 2014).*

17 Baber N. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH). *British Journal of Clinical Pharmacology* 1994; 37(5): 401-404.

18 Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Safety* 1999; 20(2): 109-117.

19 ICH M2 Expert Working Group. *Electronic transmission of individual case safety reports message specification*. International Conference on Harmonisation. Report number: ICH ICSR DTD Version 2.3, 2000.

20 The Council of the European Communities. *Council Regulation (EEC) no 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products*. European Union. Report number: 2309/93, 1993.

21 The European Parliament and the Council of the European Union. *Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*. European Union. Report number: 726/2004, 2004.

22 European Medicines Agency. *The European regulatory system for medicines and the European Medicines Agency: A consistent approach to medicines regulation across the European Union. http://www.ema.europa.eu/docs/en_GB/document_library/Brochure/2014/08/WC500171674.pdf (accessed 06 September 2014).*

23 European Medicines Agency. *Mandatory e-reporting essentials. https://eudravigilance.ema.europa.eu/human/index.asp (accessed 06 September 2014).*

24 European medicines agency. *Guideline on pharmacovigilance practice, Module VI – Management and reporting of adverse reactions to medicinal products*. European Medicines Agency. Report number: EMA/873138/2011, 2012.

25 ICH Expert Working Group. *Post-approval safety data management: definitions and standards for expedited reporting*. European Medicines Agency. Report number: CPMP/ICH/3945/03, 2004.

26 Grootheest AC van. Organisation of pharmacovigilance in the Netherlands. *Newsletter European Society of Clinical Pharmacy* 1998; 83(1): 7-8.

27 Medicines and healthcare product regulatory authority. *History of the Yellow Card scheme.*

http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/Historyofthescheme/index.htm (accessed 06 September 2014).

28 Kimland E, Rane A, Ufer M, Panagiotidis G. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. *Pharmacoepidemiology and Drug Safety* 2005; 14(7): 493-499.

29 Banerjee AK, Okun S, Edwards IR, Wicks P, Smith MY, Mayall SJ, et al. Patient-Reported Outcome Measures in Safety Event Reporting: PROSPER Consortium guidance. *Drug Safety* 2013; 36(12): 1129-1149.

30 Committee for Medicinal Products For Human Use (CHMP). *Reflection paper on the regulatory guidance for the use of health related quality of life (HRQL) measures in the evaluation of medicinal products*. European Medicine Agency. Report number: EMEA/CHMP/EWP/139391/2004, 2006.

31 Center for Drug Evaluation and Research. *Patient-reported outcome measures: use in medical product development to support labeling claims*. Food and Drug Administration. Report number: 2009, 2009.

32 McLernon DJ, Bond CM, Lee AJ, Watson MC, Hannaford MC, Fortnum H, et al. Patient views and experiences of making adverse drug reaction reports to the Yellow Card Scheme in the UK. *Pharmacoepidemiology and Drug Safety* 2011; 20(5): 523-531.

33 Krska J. Views of British community pharmacists on direct patient reporting of adverse drug reactions (ADRs). *Pharmacoepidemiology and Drug Safety* 2013; 22(10): 1130-1133.

34 Leone R, Moretti U, D'Incau P, Conforti A, Magro L, Lora R, et al. Effect of pharmacist involvement on patient reporting of adverse drug reactions: first Italian study. *Drug Safety* 2013; 36(4): 267-276.

35 The European Parliament and the Council of the European Union. *Commission implementing regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council*. European Union. Report number: 520/2012, 2012.

36 Hazell L, Cornelius V, Hannaford P, Shakir S, Avery AJ; Yellow Card Study Collaboration. How do patients contribute to signal detection? : A retrospective analysis of spontaneous reporting of adverse drug reactions in the UK's Yellow Card Scheme. *Drug Safety* 2013; 36(3): 199-206.

37 Fraunhofer Institute for Systems and Innovation Research. *Assessment of the European Community System of Pharmacovigilance*. European Commission. Report number: Final Report November 2005, 2006.

38 Nelson RC, Palsulich B, Gogolak V. Good pharmacovigilance practices: technology enabled. *Drug Safety* 2002; 25(6): 407-414.

39 van Puijenbroek EP, van Grootheest K, Diemont WL, Leufkens HG, Egberts AC. Determinants of signal selection in a spontaneous reporting system for adverse drug reactions. *British Journal of Clinical Pharmacology* 2001; 52(5): 579-586.

40 EudraVigilance Expert Working Group. *Note for guidance - EudraVigilance Human - Processing of safety messages and individual case safety reports (ICSRs)*. European Medicines Agency. Report number: EMA/H/20665/04/Final Rev. 2, 2010.

41 Lindquist M. Use of triage strategies in the WHO signal-detection process. *Drug Safety* 2007; 30(7): 635-637.

42 Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Safety* 2006; 29(5): 385-396.

43 Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. *Drug Safety* 2009; 32(1): 19-31.

44 Edwards IR. Spontaneous reporting--of what? Clinical concerns about drugs. *British Journal of Clinical Pharmacology* 1999; 48(2): 138-141.

45 Härmark L, van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. *European Journal of Clinical Pharmacology* 2008; 64(8): 743-752.

46 Clarke A, Deeks JJ, Shakir SA. An assessment of the publicly disseminated evidence of safety used in decisions to withdraw medicinal products from the UK and US markets. *Drug Safety* 2006; 29(2): 175-181.

47 Eland IA, Belton KJ, van Grootheest AC, Meiners AP, Rawlins MD, Stricker BH. Attitudinal survey of voluntary reporting of adverse drug reactions. *British Journal of Clinical Pharmacology* 1999; 48(4): 623-627.

48 European Commission. *Demographic balance and crude rates. http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_gind&lang=en (accessed 20 December 2010).*

49 The Organisation for Economic Co-operation and Development (OECD). *Health policies and data. http://www.oecd.org/els/health-systems/health-data.htm (accessed 15 July 2011).*

50 Meyboom RH, Egberts AC, Gribnau FW, Hekster YA. Pharmacovigilance in perspective. Drug Safety 1999; 21(6): 429-447.

51 Office of the Executive Director. *Annual report 2009*. European Medicines Agency. Report number: EMA/MB/69923/2010, 2010.

52 World Health Organization. *World health statistics 2010*. World Health Organization. Report number: 2010, 2010.

53 The Danish Medicines Agency. *The Danish Medicines Agency's annual pharmacovigilance report 2009*. The Danish Medicines Agency. Report number: 2009, 2010.

54 The Medical Products Agency. *Hälso- och sjukvårdens inrapporterade biverkningar 2009*. The Medical Products Agency. Report number: 2009, 2010.

55 Irish Medicines Board. *Annual report 2008. Protecting public and animal health*. Irish Medicines Board. Report number: 2008, 2009.

56 Icelandic Medicines Agency. *Annual report 2009*. Icelandic Medicines Agency. Report number: 2009, 2010.

57 Norwegian Medicines Agency. *Bivirkningsrapport for 2009. http://www.legemiddelverket.no/Nyheter/Bivirkninger/Sider/Bivirkningsrapport-for-2009.aspx (accessed 26 December 2010).*

58 Breeveld L, Voorhorst M, Jongejan A. *Annual report*. Medicines Evaluation Board (CBG-MEB). Report number: 2009, 2010.

59 Malta Medicines Authority. *Annual report*. Malta Medicines Authority. Report number: 2009, 2010.

60 Medicines and Healthcare products Regulatory Agency. *MHRA annual statistics 2009/10*. Medicines and Healthcare products Regulatory Agency. Report number: 2009, 2010.

61 French Agency for the Safety of Health Products. *Afssaps: Repport annuel 2009*. French Agency for the Safety of Health Products. Report number: 2009, 2010.

62 Müllner M. *Jahresbericht PharmMed 2009*. Austrian Agency for Health and Food Safety. Report number: 2009, 2010.

63 De Cuyper X. *The FAMHP moves up agear. Annual report 2009*. Federal Agency for Medecines and Health Products. Report number: 2009, 2010.

64 AEMPS. *Memoria de actividades de la AEMPS*. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Report number: E-28022, 2010.

65 Priya B, Panos T, Waller PC (2007) Regulatory pharmacovigilance in the EU. (pp 185–98) Pharmacovigilance, 2nd edn. John Wiley & Sons, Chichester,

66 Alemayehu D. Evaluation of reporting bias in postmarketing risk assessment based on spontaneous reporting systems. *Pharmaceutical Medicine* 2009; 4(23): 195–200.

67 Lindquist M. Use of triage strategies in the WHO signal detection process. *Drug Safety* 2007; 30(7): 635–637.

68 Lindquist M. Data quality management in pharmacovigilance. *Drug Safety* 2004; 27(12): 857–870.

69 Lindquist M, Stahl M, Bate A, Edwards IR, Meyboom RH. A retrospective evaluation of a data mining approach to aid fading new adverse drug reaction signals in the WHO international database. *Drug Safety* 2010; 23(6): 533-542.

70 Biagi C, Motola D. *Farmacosorveglianza: la segnalazione delle reazioni avverse da farmaci in Emilia-Romagna nel 2008*. Centro Regionale di Valutazione e Informazione Sui Farmaci. Report number: Luglio 2009, 2009.

71 Butt TF, Cox AR, Lewis H, Ferner RE, et al. Patient experiences of serious adverse drug reactions and their attitudes to medicines: a qualitative study of survivors of Stevens-Johnson syndrome and toxic epidermal necrolysis in the UK. *Drug Safety* 2011; 34(4): 319-328.

72 McLernon DJ, Bond CM, Hannaford PC, Watson MC, Lee AJ, Hazell L, et al. Adverse drug reaction reporting in the UK: a retrospective observational comparison of yellow card reports submitted by patients and healthcare professionals. *Drug Safety* 2010; 33(9): 775-788.

73 Blenkinsopp A, Wilkie P, Wang M, Routledge PA. Patient reporting of suspected adverse drug reactions: a review of published literature and international experience. *British Journal of Clinical Pharmacology* 2007; 63(2): 148-156.

74 Anton C, Cox AR, Ferner RE. Improving follow-up rates in spontaneous adverse drug reaction reporting: effectiveness of a targeted letter used by a regional centre in the UK. *Drug Safety* 2009; 32(12): 1135–1140.

75 Gony M, Badie K, Sommet A, Jacquot J, Baudrin D, Gauthier P, et al. Improving adverse drug reaction reporting in hospitals: results of the French Pharmacovigilance in Midi-Pyrénées region (PharmacoMIP) network 2-year pilot study. *Drug Safety* 2010; 33(5): 409-416.

76 European Union. *33 Regulation (EU) No 1235/2010 of the European Parliament and of the council of 15 December 2010, amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 and Regulation (EC) No 1394/2007*. European Union. Report number: 1235/2010, 2010.

77 European Union. *34 Directive 2010/84/EU of the European Parliament and of the council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use*. European Union. Report number: 2010/84/EU, 2010.

78 van Grootheest K, de Graaf L, de Jong-van den Berg LT. Consumer adverse drug reaction reporting: a new step in pharmacovigilance? *Drug Safety* 2003; 26(4): 211-217.

79 Vincent CA, Coulter A. Patient safety: what about the patient? *Quality & Safety in Health Care* 2002; 11(1): 76-80.

80 Herxheimer A, Crombag R, Alves TL. *Direct patient reporting of adverse drug reactions: a fifteen-country survey & literature review*. Health Action International (Europe). Report number: 01-2010/05, 2010.

81 van Hunsel F, Härmark L, Pal S, Olsson S, van Grootheest K. Experiences with adverse drug reaction reporting by patients: an 11-country survey. *Drug Safety* 2012; 35(1): 45-60.

82 van den Bemt PM, Egberts AC, Lenderink AW, Verzijl JM, Simons KA, van der Pol WS, et al. Adverse drug events in hospitalized patients. A comparison of doctors, nurses and

patients as sources of reports. *European Journal of Clinical Pharmacology* 1999; 55(2): 155-158.

83 Jarernsiripornkul N, Krska J, Capps PA, Richards RM, Lee A. Patient reporting of potential adverse drug reactions: a methodological study. *British Journal of Clinical Pharmacology* 2002; 53(3): 318-325.

84 Moher D, Liberati A, Tetzlaff J, Altman DG (2009) PRISMA Group. Reprint—preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Physical Therapy 89: 873-880.

85 Avery AJ, Anderson C, Bond CM, Fortnum H, Gifford A, Hannaford PC, et al. Evaluation of patient reporting of adverse drug reactions to the UK 'Yellow Card Scheme': literature review, descriptive and qualitative analyses, and questionnaire surveys. *Health Technology Assessment* 2011; 15(20): 1-234.

86 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009; 6(7): 1-28.

87 de Langen J, van Hunsel F, Passier A, de Jong-van den Berg L, van Grootheest K. Adverse drug reaction reporting by patients in the Netherlands: three years of experience. *Drug Safety* 2008; 31(6): 515-524.

88 van Hunsel F, Passier A, van Grootheest K. Comparing patients' and healthcare professionals' ADR reports after media attention: the broadcast of a Dutch television programme about the benefits and risks of statins as an example. *British Journal of Clinical Pharmacology* 2009; 67(5): 558-564.

89 Aagaard L, Nielsen LH, Hansen EH. Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. *Drug Safety* 2009; 32(11): 1067-1074.

90 Inch J, Watson MC, Anakwe-Umeh S, et al. Patient versus healthcare professional spontaneous adverse drug reaction reporting: a systematic review. *Drug Safety* 2012; 35(10): 807-818.

91 Patel P, Zed PJ. Drug-related visits to the emergency department: how big is the problem? *Pharmacotherapy* 2002; 22(7): 915-923.

92 Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18.820 patients. *British Medical Journal* 2004; 329(7456): 15-19.

93 Wester K, Jonsson AK, Spigset O, Druid H, Hagg S. Incidence of fatal adverse drug reactions: a population based study. *British Journal of Clinical Pharmacology* 2008; 65(4): 573-579.

94 Goldman SA. Limitations and strengths of spontaneous reports data. *Clinical Therapeutics* 1998; 20(1): 40-44.

95 Anderson C, Krska J, Murphy E, Avery A. The importance of direct patient reporting of suspected adverse drug reactions: a patient perspective. Yellow Card Study Collaboration. *British Journal of Clinical Pharmacology* 2011; 72(5): 806-822.

96 van Grootheest K, de Jong-van den Berg L. Patients' role in reporting adverse drug reactions. *Expert Opinion on Drug Safety* 2004; 2(4): 363-368.

97 Aagaard L, Hansen EH. Side effects of antineoplastic and immunomodulating medications reported by European consumers. *Journal of Research in Pharmacy Practice* 2013; 2(1): 44-49.

98 Aagaard L, Hansen EH. Adverse drug reactions reported by consumers for nervous system medications in Europe 2007 to 2011. *BMC Pharmacology & Toxicology* 2013; 14(1): 30.

99 European Medicines Agency. *National competent authorities (human). http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp&mid=WC0b01ac0580036d63 (accessed 20 September 2014).*

100 Arimone Y, Bégaud B, Miremont-Salamé G, Fourrier-Réglat A, Moore N, Molimard M, et al. Agreement of expert judgment in causality assessment of adverse drug reactions. *European Journal of Clinical Pharmacology* 2005; 61(3): 169-173.

101 Macedo AF, Marques FB, Ribeiro CF. Can decisional algorithms replace global introspection in the individual causality assessment of spontaneously reported ADRs? *Drug Safety* 2006; 29(8): 697-702.

102 Vilhelmsson A, Svensson T, Meeuwisse A, Carlsten A. Experiences from consumer reports on psychiatric adverse drug reactions with antidepressant medication: a qualitative study of reports to a consumer association. *BMC Pharmacology & Toxicology* 2012; 13(1): 19.

103 Bent S, Padula A, Avins AL. Brief communication: Better ways to question patients about adverse medical events: a randomized, controlled trial. *Annals of Internal Medicine* 2006; 144(4): 257–261.

104 de Vries ST, Mol PG, de Zeeuw D, Haaijer-Ruskamp FM, Denig P. Development and Initial Validation of a Patient-Reported Adverse Drug Event Questionnaire. *Drug Safety* 2013; 36(9): 765-777.

105 European Commission. *Households having access to the Internet, by type of connection. http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&plugin=0&language=en&pcode=tin00073 (accessed 20 September 2014).*

106 Harmark L, Puijenbroek E, Grootheest K. Longitudinal monitoring of the safety of drugs by using a web-based system: the case of pregabalin. *Pharmacoepidemiology and Drug Safety* 2011; 20(6): 591–597.

107 Meyboom RHB, Royer RJ. Causality Classification in Pharmacovigilance Centres in the European Community. *Pharmacoepidemiology and Drug Safety* 1992; 1(2): 87-97.

108 Borg JJ, Aislaitner G, Pirozynski M, Mifsud S. Strengthening and rationalizing pharmacovigilance in the EU: where is Europe heading to? A review of the new EU legislation on pharmacovigilance. *Drug Safety* 2011; 34(3): 187-197.

109 Wright KB. Researching internet-based populations: advantages and disadvantages of online survey research, online questionnaire authoring software packages, and web survey services. Journal of Computer-Mediated Communication 2005; 10(3): 00-00.

110 Margraff F, Bertram D. Adverse drug reaction reporting by patients: an overview of fifty countries. *Drug Safety* 2014; 37(6): 409-419.

111 Banerjee AK, Ingate S. Web-based patient-reported outcomes in drug safety and risk management: challenges and opportunities? *Drug Safety* 2012; 35(6): 437-446.

112 Swan M. Emerging patient-driven health care models: an examination of health social networks, consumer personalized medicine and quantified self-tracking. *International Journal of Environmental Research and Public Health* 2009; 6(2): 492-525.

113 Chee BW, Berlin R, Schatz B. Predicting adverse drug events from personal health messages. *AMIA Annual Symposium Proceedings* 2011; 2011(1): 217-26.

114 Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. *Drug Safety* 2013; 36(2): 75-81.

115 Rolfes L, Wilkes S, van Hunsel F, van Puijenbroek E, van Grootheest K. Important information regarding reporting of adverse drug reactions: a qualitative study. *International Journal of Pharmacy Practice* 2014; 22(3): 231-233.

116 De Vries ST, Haaijer-Ruskamp FM, de Zeeuw D, Denig P. The validity of a patient-reported adverse drug event questionnaire using different recall periods. *Quality of Life Research* 2014; [Epub ahead of print].

117 Alvarez Y, Hidalgo A, Maignen F, Slattery J. Validation of statistical signal detection procedures in eudravigilance post-authorization data: a retrospective evaluation of the potential for earlier signalling. *Drug Safety* 2010; 33(6): 475-487.

8. Abbreviations

ADR	Adverse Drug Reaction
EEA	European Economic Area
EMA	European Medicines Agency
HP	Healthcare Professionals
MAH	Marketing Authorization Holder
MS	Member State
NCA	National Competent Authority
PBRR	Population Based Reporting Ratio
PRO-AE	Patient Reported Outcomes of Adverse Event
RYM	Reports per year per million inhabitants
SRS	Spontaneous Reporting System

9. List of published scientific papers

9.1. Related to pharmacovigilance issue

- Srba J. The missing voice of non-serious adverse drug reactions from marketing authorization holders. *Advances in Pharmacoepidemiology & Drug Safety* 2014; 3(2): 154.
- Srba J, Vlcek J. Position and processing of adverse drug reactions directly submitted by patients to national regulatory authorities in Europe. *Journal of Pharmacovigilance* 2014; 2(1): 122.
- Srba J, Descikova V, Vlcek J. Adverse drug reactions: Analysis of spontaneous reporting system in Europe in 2007-2009. *European Journal of Clinical Pharmacology* 2012; 68(1): 1057-1063.

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  IF (at the time of acceptance for publication): 2,741

9.2. Not related to pharmacovigilance

- Franta Z, Sojka D, Frantova H, Dvorak J, Horn M, Srba J, et al. IrCL1 – The haemoglobinolytic cathepsin L of the hard tick, Ixodes ricinus. *International Journal of Parasitology* 2011; 41(12): 1253-1262.

  ISSN: 0020-7519

  IF (at the time of acceptance for publication): 3,404

- Horn M, Nussbaumerova M, Sanda M, Kovarova Z, Srba J, Franta Z, et al. Hemoglobin digestion in blood-feeding ticks: mapping a multipeptidase pathway by functional proteomics. *Chemistry & Biology* 2009; 16(10): 1053-1063.

  ISSN: 1074-5521

  IF (at the time of acceptance for publication): 6,523

10. Attendance on seminars

April 2011	State Authority for Drug Control (1 day) Pharmacovigilance inspection Following issues were covered: • Preparation for inspection. • Types of inspections. • Inspected area.
October 2011	Drug Information Association (3 days) EudraVigilance – electronic reporting of ICSRs The primary goals of this course were to: • Acquire a knowledge in the fundamentals of the electronic reporting of ICSRs. • Familiarise with the electronic transmission of ICSRs and the ICH M2 safety and acknowledgment message specifications. • Experience with the EudraVigilance reporting capabilities and query functions.
January 2012	Drug Information Association (2 days) Extended EudraVigilance Medicinal Product Dictionary (xEVMPD) The primary goals of this course were to understand: • General terms and definitions, EVMPD data elements, operation types, data quality, data ownership. • xEVMPD database architecture, product report database, scientific product, product index database. • xEVMPD and adverse reaction reporting in EudraVigilance. • How to enter and maintain product data in the xEVMPD. • Validation process by EMA. • How to query the xEVMPD. • Simple Access database.
June 2012	State Authority for Drug Control (1 day) Pharmacovigilance Following issues were covered: • Risk management plan. • Periodic safety update reports. • Pharmacovigilance system master file. • Adverse drug reaction.

	• Non-interventional post-authorization safety studies of medicinal products for human use.
October 2012	Slovak Association of Regulatory Affairs Professionals (1 day) Pharmacovigilance Following issues were covered: • Reporting of adverse drug reactions. • The new legislation on pharmacovigilance. • Post-authorization safety studies. • Preparation and administration PSUR periodicity. • The system of pharmacovigilance and inspection.
October 2012	Drug Information Association (2 days) Benefit/Risk Management Following issues were covered: • Regulatory tools, including EU Risk Management Plans, Risk Evaluation and Mitigation Strategies, Development Safety Update Report, Periodic Safety Update Report, Follow-Up Measures, and EU Benefit Risk Management Plan. • How to measure their effectiveness. • Situations when benefit/risk of the product is at stake and you need to manage a media, legal and regulatory crisis.
May 2013	State Authority for Drug Control (1 day) Pharmacovigilance and amendment of the Act on Pharmaceuticals Following issues were covered: • Pharmacovigilance system. • Non-interventional post-authorization safety studies of medicinal products for human use. • Electronic reporting of ICSRs. • Risk management system • Risk management plan.
December 2013	State Authority for Drug Control (1 day) Variations performed after the 4th August 2013 at nationally authorized medicines Following issues were covered: • Grouping/work-sharing in variations. • How to prepare texts of high quality. • Fees for variations. • Procedures related to variations. • Variations – type C. • Submission of variation.
June 2014	State Authority for Drug Control (1 day)

Amendment to the Act on Pharmaceuticals, European Pharmacovigilance Legislation and other changes related to pharmacovigilance

Following issues were covered:

- Pharmacovigilance system master file.
- Risk management plan.
- Educational materials and dear healthcare professional letter.
- Reporting Individual Case Safety Reports.
- Post-authorization safety studies.
- Additional monitoring.
- Pharmacovigilance signals.
- Periodic safety update reports.

11. Figures

12. Tables

13. Abstract

Introduction: Pharmacovigilance system is consisted of several approaches used for drug safety surveillance. Spontaneous reporting systems in European countries have been established in the second half of the 20th century. Originally, spontaneous collection of adverse drug reactions was designed for healthcare professionals. Under-reporting was in general considered as the main weakness of spontaneous reporting system. To increase the reporting activity, direct patient reporting has been included in spontaneous reporting system at national competent authorities.

Aims: The aim of this work was to characterize spontaneous reporting system. Subsequently, we focused on the evaluation of position of patient-reported outcomes of adverse events (PRO-AE) in established systems of the European countries. In particular, we i) characterized reporting activity within European countries, ii) evaluated the position of adverse drug reaction (ADR) reports directly submitted by patients to national competent authorities, and iii) overviewed of the processing of PRO-AEs.

Methodology: Practical part was based on questionnaires distributed to national competent authorities and literature search of electronic databases with relevant published articles.

Results: Characterization and comparison of national spontaneous reporting systems were based on population based reporting ratio. Increase in reporting activity at national and international level throughout the years was detected. Many factors may influence spontaneous reporting activity, nevertheless legal obligation of healthcare professionals to report any ADR did not correlate with the increase of reporting activity across the European countries.

PRO-AEs became very important in the framework of spontaneous reporting system. Various attitudes to direct patient reporting were detected among respective national competent authorities. Available studies concerned to the comparison reports coming from healthcare

professionals or directly from patients reflected various outcomes. After legislation requirement to accept PRO-AEs, which came into force in 2012, issues like medical and reporter validation should be solved.

Conclusion: Spontaneous reporting system is indispensable tool used by national competent authorities to collect ADR reports. Establishment direct patient reporting in the current spontaneous reporting systems brought both opportunities and potential complications due to specific characterstics of patients as reporters.

11. Abstrakt

Úvod: Farmakovigilance využívá několika nástrojů pro dohled nad bezpečností léčiv. Systémy spontánního hlášení v evropských zemích byly založeny ve druhé polovině 20. století. Původně bylo spontánní hlášení nežádoucích účinků určeno pouze pro lékaře. Nedostatečné hlášení je obecně považováno za hlavní slabinu tohoto systému. Z důvodu zvýšení počtu hlášení začaly regulační autority přijímat hlášení také přímo od pacientů.

Cíle: Cílem této práce bylo charakterizovat farmakovigilanční systém hlášení nežádoucích účinků. Zaměřili jsme se na hodnocení pozice pacientů jako přímý zdroj hlášení nežádoucích účinků (PRO-AE) v zavedených systémech evropských zemí. Dílčí cíle byli i) charakterizovat aktivity hlášení v rámci evropských zemí, ii) zhodnotit pozici pacientů jako přímý zdroj hlášení nežádoucích účinků, a iii) zpracovat přehled o přístupu regulačních autorit k hlášení nežádoucích účinků přímo pacienty.

Metodika: Praktická část byla založena na dotaznících distribuovaných na příslušné národní kompetentní autority, a na rešerši elektronických databází s relevantními publikovanými články.

Výsledky: Charakterizace a srovnávání národních systémů hlášení nežádoucích účinků bylo založeno na poměru počtu hlášení na obyvatele. V průběhu let rostl počet hlášení jak na národní, tak a mezinárodní úrovni. Počet zpráv s nežádoucími účinky zaslané na kompetentní autority je ovlivněn mnoha faktory, nicméně legislativní povinnosti zdravotnických pracovníků hlásit nežádoucí účinek neměla vliv na počet zaslaných zpráv na kompetentní autority v jednotlivých evropských zemích.

Přímá pacientská hlášení se stala velmi důležitým prvkem v rámci systému spontánního hlášení nežádoucích účinků. Mezi jednotlivými kompetentními autoritami byly zjištěny různé postoje k přímému hlášení nežádoucích účinků pacienty. Dostupné studie, které se zabývaly

porovnáním zpráv s nežádoucími účinky zaslané lékaři nebo přímo pacienty, dochází k různým závěrům. Po zavedení legislativního požadavku přijímat hlášení zaslaná přímo pacienty, který vstoupil v platnost v roce 2012, je potřeba se zaměřit na témata jako jsou odborná validace zpráv nebo validace zdroje hlášení.

Závěr: Systém spontánního hlášení je nezbytný nástroj používaný kompetentními autoritami evropských států při shromažďování nežádoucích účinků. Zavedení přímého hlášení od pacientů v současném systému hlášení přinesl vedle nových možností i potenciální komplikace, které vycházejí z podstaty pacienta jako specifického zdroje hlášení.