Drug Saf (2014) 37:1059–1066
DOI 10.1007/s40264-014-0240-1

ORIGINAL RESEARCH ARTICLE

A Description of Signals During the First 18 Months of the EMA Pharmacovigilance Risk Assessment Committee

Alexandra C. Pacurariu · Preciosa M. Coloma · Anja van Haren · Georgy Genov · Miriam C. J. M. Sturkenboom · Sabine M. J. M. Straus

Published online: 15 November 2014

Abstract

Background and Objective New pharmacovigilance legislation in the European Union has underlined the importance of signal management, giving the European Medicines Agency's newly established Pharmacovigilance Risk Assessment Committee (PRAC) the mandate to oversee all aspects of the use of medicinal products including detection, assessment, minimization, and communication relating to the risk of adverse reactions. In this study, we describe the signals as brought to the PRAC during the first 18 months of its operation and the ensuing regulatory actions.

Methods Data were collected from publicly available sources, for the period July 2012–December 2013, classified according to predefined rules, and described using the appropriate descriptive statistics. Suspected adverse drug reactions were categorized into the *Medical Dictionary for Regulatory Affairs* and drug names were mapped to the Anatomical Therapeutic Chemical codes.

Results During the study period, 125 signals concerning 96 medicinal products were discussed by the PRAC. The majority of signals were triggered by spontaneous reports (62 %) and the median drug age (since marketing authorization) for drugs that prompted a signal was 12 years, significantly less compared with drugs that had no signal within the same period (20 years). The mean time until a decision was reached by the PRAC was 75 days (median 30 days, range 0–273) with 43 % of all decisions taken during the first meeting. The decisions to start a referral and to send a direct healthcare professional communication took the least amount of time [54 days (median 27 days, range 0–186) and 51 days (median 0 days, range 0–153)].

Conclusions The importance of spontaneous reporting in signal detection and monitoring of safety issues throughout the entire life cycle of a medicinal product is confirmed in this study. The amount of time a drug has been on the market is correlated with the number of signals detected. The PRAC decision-making process seems efficient particularly with respect to serious concerns; its role in improving signal prioritization and real-time signal management will be further clarified in its subsequent years of operation.

Key Points

Spontaneous reports remain an important source of safety signals.

The amount of time of a drug on the market ('drug age') is correlated with the number of signals detected.

This could be considered, alongside other variables, when determining the frequency of monitoring.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-014-0240-1) contains supplementary material, which is available to authorized users.

A. C. Pacurariu · P. M. Coloma · M. C. J. M. Sturkenboom · S. M. J. M. Straus
Department of Medical Informatics, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands

A. C. Pacurariu · A. van Haren · S. M. J. M. Straus (✉)
Dutch Medicines Evaluation Board, Utrecht, The Netherlands
e-mail: sm.straus@cbg-meb.nl

G. Genov
European Medicines Agency, London, United Kingdom

1 Introduction

Pre-approval clinical research is primarily focused on establishing efficacy, and its limitations with regard to identifying risks are well known and described previously [1–3]. Only after market exposure and use in everyday practice is more information on the full benefit–risk profile identified.

An important cornerstone in further clarifying the risk profile of a medical product post-marketing is the detection of 'signals', that is, "information which arise from one or multiple sources (including observation and experiments), which suggest a new potentially causal association or a new aspect of a known association, between an intervention and a set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory action" [4]. In pharmacovigilance, we are primarily concerned with safety signals. Safety signals may arise anytime during the drug lifecycle but they are expected to occur more frequently in the first years of marketing [4]. However, also after several years new adverse events can arise.

Within the context of the new pharmacovigilance legislation in the European Union (EU), this key initial stage in the pharmacovigilance process is now duly recognized and specific responsibilities and interactions between stakeholders have been laid down in several guidance documents [5, 6]. According to the current legislation, the marketing authorization holders, the European Medicines Agency (EMA) and the national competent authorities "should continuously monitor the data available in the EudraVigilance database" [6, 7].

The Pharmacovigilance Risk Assessment Committee (PRAC) [8] at the EMA has a central role in scientific advice and decision making in relation to signal management. The mandate of the PRAC covers all aspects of risk management of the use of medicinal products for human use including the detection, assessment, minimization, and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorization safety studies, and a pharmacovigilance audit [6, 7, 9].

In the EU, the signal management process concerns all stakeholders involved in the safety monitoring of medicinal products including patients, healthcare professionals, marketing authorization holders, regulatory authorities, scientific committees, and decision-making bodies (such as competent authorities in the Member States and the European Commission). Whereas the EudraVigilance database is a major source of pharmacovigilance information, the signal management process covers also signals arising from outside the EudraVigilance database or not directly supported by this database. The legislation [6, 7] has laid down the specific requirements for the different stakeholders. In the Good Vigilance Practice module IX, detailed information and guidance is provided including the different roles and responsibilities of the stakeholders [5, 20].

The signals on the PRAC agenda are generated by the EMA or member states. If the marketing authorization holders identify a signal, they cannot send it directly to the PRAC, but to national agencies or the EMA, who will further decide the way of handling. The criteria for referring a signal to the PRAC are not specifically set, except those derived from current guidelines [5], namely a signal should be new and clinically significant.

For signal management, the PRAC has an important role in the prioritization of potentially new safety issues, evaluating the underlying data and making recommendations regarding the regulatory actions that should be taken [5, 9].

2 Objectives

The objective of this study was to characterize the signals as brought to the PRAC during the first 18 months of its operation (July 2012–December 2013) and the ensuing regulatory actions. Within this characterization we focused on factors related to the lifecycle of a drug (e.g., time since marketing authorization).

3 Methods

3.1 Data Collection

Data regarding the safety signals were extracted from the publicly available information on the website of the EMA containing the PRAC meeting minutes and recommendations on safety signals [10, 11]. Suspected adverse drug reactions were categorized using the *Medical Dictionary for Regulatory Affairs* (terminology, version 16.1), an international medical terminology developed under the auspices of the International Conference on Harmonization [12]. International nonproprietary names of drugs were mapped to the Anatomical Therapeutic Chemical classification codes according to the World Health Organization classification and the first authorization date was collected from European Union Reference Date list, when not available from the EMA website or other regulatory resources. For class effects, the oldest substance was used as a reference for calculating the time since marketing

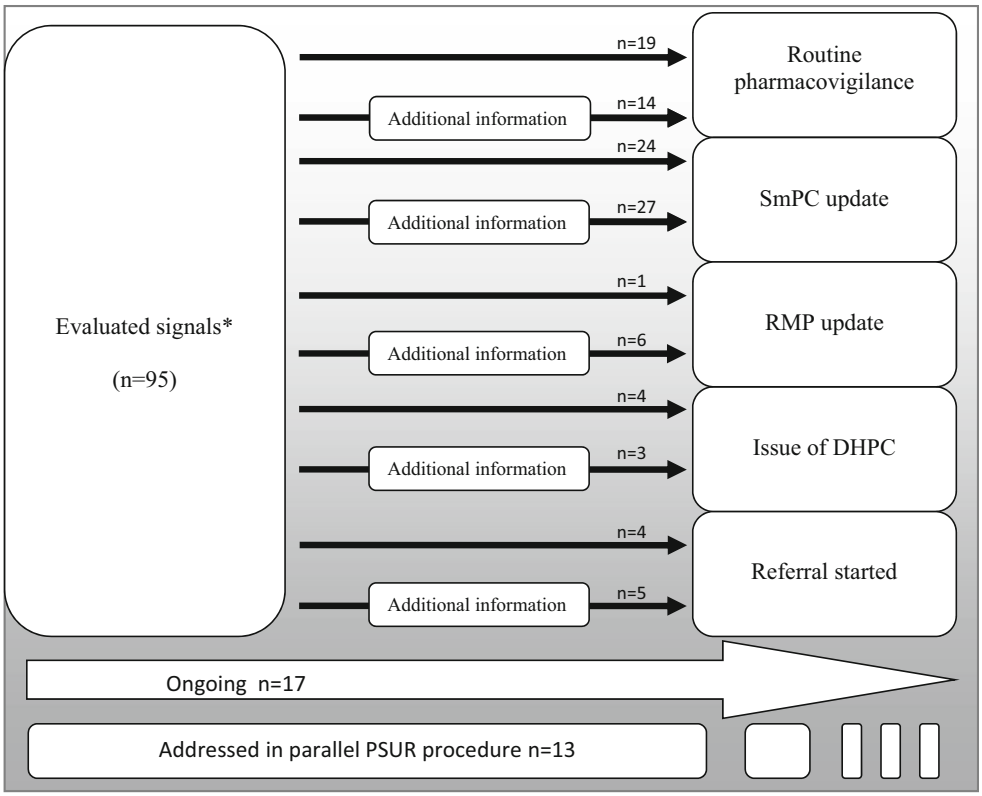

Fig. 1 Workflow of signals at the PRAC. *DHPC* dear healthcare professional communication, *PRAC* Pharmacovigilance Risk Assessment Committee, *PSUR* periodic safety update report, *RMP* risk management plan, *SmPC* summary of product characteristics, *asterisk* represents more than one recommendation per signal possible

authorization. Data on medical product exposure were likewise obtained from PRAC meeting minutes.

3.2 Classification of Variables

Signals are classified, by default, to be derived from either EU spontaneous reporting systems (Eudravigilance or national) or other sources. However, to provide more detailed information on the source of the signals, we employed the following classification for this study: (1) spontaneous case reports; (2) spontaneous case reports plus published cases; (3) clinical trials; (4) observational studies; (5) published case reports or case series; and (6) others. Communications from other regulatory authorities outside the EU were tracked, when possible, to determine the original source.

The medical products were classified according to the type of authorization: centralized authorization (i.e., single marketing authorization across all EU countries) or national authorization (i.e., the product is authorized at a national level in one or more member states).

PRAC recommendations were collected and categorized according to the action taken. After a signal is brought to the PRAC for discussion, these are the possible outcomes: (1) no further action besides routine pharmacovigilance; (2) request for further data; or (3) immediate action. Further evaluation in an ongoing periodic safety update reports (PSURs) assessment was considered a separate and temporary outcome. The recommendation for cumulative reviews to be provided in future PSURs was considered routine pharmacovigilance. The regulatory actions that can be taken after a signal is discussed include: (1) update of summary of product characteristics; (2) direct communication to healthcare professionals; (3) update of the risk management plans; (4) suspension/withdrawal from the market; or (5) re-evaluation of the benefit–risk profile through a referral procedure (see Fig. 1). It is possible to have more than one regulatory action per signal. In this study, we considered an action as immediate if the decision was taken in the first PRAC meeting. Signals for which the outcome was not available in the month after the end of the study period (i.e., January 30, 2014) were labeled as ongoing.

3.3 Data Analysis

Descriptive statistics appropriate to the type of variables were used to describe the characteristics of signals discussed at the PRAC during the study period.

We also tested the hypothesis that drugs that had signals in the study period were 'younger' than those that did not have signals. For this purpose, we compared the drugs that had at least one signal on the PRAC agenda during the study period with a set of controls comprising drugs

Table 1 Characteristics of signals discussed at the PRAC between July 2012 and December 2013

Signals, *n*	125[a]
Medicinal products, *n*	96
Identifier count, *n* (%)	
European Medicines Agency	65 (52)
Individual member states (country of origin)	
Netherlands	15 (12)
United Kingdom	15 (12)
Italy	7 (5.6)
Sweden	5 (4.0)
France	4 (3.2)
Belgium	3 (2.4)
Denmark	3 (2.4)
Ireland	3 (2.4)
Germany	2 (1.6)
Spain	1 (0.8)
Finland	1 (0.8)
Portugal	1 (0.8)
Time since marketing authorization, years (%)	
Median (range)	12 (0.5–68)
≤5	20 (21)
5–10	20 (21)
≥10–15	16 (17)
≥15	40 (41)
Type of authorization count, *n* (%)[b]	
Centralized	49 (51)
National	41 (43)
Mixed	6 (6.3)
Signals of special interest count, *n* (%)	
Drug interaction	13 (10)
Medication error	2 (1.6)
Off-label use	2 (1.6)
In utero exposure	2 (1.6)
Accidental exposure	1 (0.8)
Source, *n* (%)	
Spontaneous cases	77 (62)
Spontaneous cases including literature case reports	13 (10)
Randomized controlled trials	10 (8.0)
Observational (post-marketing) studies	10 (8.0)
Literature case reports	8 (6.4)
Other	7 (5.6)
System Organ Class, *n* (%)[c]	
Skin and subcutaneous tissue disorders	16 (13)
Nervous system disorders	13 (10)
Cardiac disorders	8 (6.4)
Immune system disorders	8 (6.4)
Blood and lymphatic system disorders	7 (5.6)
Investigations	7 (5.6)
Vascular disorders	7 (5.6)
Other (less than 5 %)	59 (47)
Drug class, *n* (%)	
Antineoplastic and immunomodulators	25 (26)
Nervous system	20 (21)
Anti-infective for systemic use	13 (14)
Alimentary tract and metabolism	5 (5.2)
Other	33 (34)

ATC Anatomic Therapeutic Chemical classification, *Identifier* the country that sends the initial signal to the PRAC, *MedDRA Medical Dictionary for Regulatory Affairs*, *PRAC* Pharmacovigilance Risk Assessment Committee

[a] Three signals were not counted for the following reasons: two were considered a duplication of a same signal for a different vaccine strain (primary ovarian failure and complex regional pain syndrome with human papilloma virus vaccines) and another one (boceprevir and drug interaction with quetiapine) was extended (considered class effect) from an already discussed signal

[b] Centralized authorization: a single marketing authorization that is valid in all European Union countries, National authorization: the product is authorized and marketed in one or more member state(s), Mixed: a combination of centralized and national authorization

[c] System organ class: classification of an adverse reaction according to its etiology and manifestation site in anatomic site in MedDRA terminology

monitored during the same period but that did not yield any signal considered at the PRAC. These controls were chosen from the signal work-sharing list (a list of active substances contained in authorized medicines for which a lead Member State has been appointed to monitor data in EudraVigilance, to validate and confirm signals on behalf of the EU regulatory network) [13] and from the list of centralized products monitored by the EMA. In the case of a signal work-sharing list, to correct for potential variations in applying monitoring methodologies between countries, drugs were matched on a Lead Member State (i.e., a country responsible for monitoring of a particular drug) to ensure that they underwent the same screening process.

4 Results

During the study period of July 2012–December 2013, 125 signals were discussed by PRAC, for 96 different drugs. Among the 125 signals, 15 were follow-ups from the previous Pharmacovigilance Working Party (i.e., former scientific group that handled signals at the EMA before establishment of PRAC) discussion.

A descriptive analysis of all signals discussed at the PRAC is presented in Table 1. The majority of signals were triggered by spontaneous reports (62 %), followed by spontaneous reports plus literature case-series (10 %), clinical trials (8 %), and observational studies (8 %). Ten signals (8 %) originated from regulatory authorities outside

Europe. The most frequently discussed signals were related to skin and subcutaneous tissue disorders (13 %), nervous system disorders (10 %), cardiac disorders (6.4 %), and immune system disorders (6.4 %). The median time since the first marketing authorization in a European country for the drugs discussed at the PRAC was 12 years (range 0.5–68), with 42 % being less than 10 years on the market (see Fig. 2). If we exclude signals at a class level from the analysis, the distribution of time on the market is shifted towards the left, the median being 1 year lower; 11 years (see electronic supplementary material).

Exposure data were available for 75 % of drugs; however, it was variously reported as either the number of patients (42 %) or person-years (33 %) and across different time periods and therefore not directly comparable between drugs. From the comparable data, the median cumulative exposure from the marketing authorization until the signal date was 2.1 million patients (range 3,000–320 million patients), the majority of drugs (68 %) having an exposure of less than 10 million patients.

Table 2 summarizes PRAC final recommendations regarding signals and the time from the first discussion until the decision. Signals under ongoing evaluation ($n = 17$, 13 %) and those addressed in parallel procedures were excluded from the time analysis, because no final outcome was reached for those at the time of writing of this article. The mean time-to-PRAC decision for a signal was 75 days (median 30 days, range 0–273 days) with 43 % of all decisions taken during the first meeting (i.e., immediate action). For 17 % of signals concluded in the first meeting, no action besides routine pharmacovigilance was needed. We performed a sensitivity analysis where we included the decision to address the signals in ongoing PSURs in the calculation; for this we obtained a mean time-to-PRAC decision of 66 days (median 0 days, range 0–273 days) with 54 % immediate actions taken.

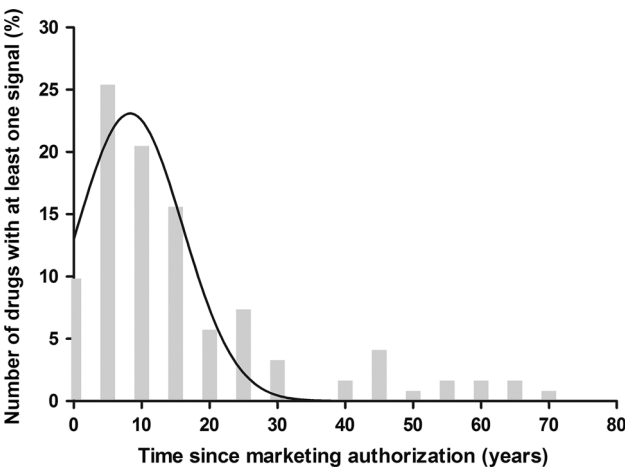

Fig. 2 Time since marketing authorization across drugs that had a signal on the PRAC agenda. *PRAC* Pharmacovigilance Risk Assessment Committee

Table 2 PRAC final recommendations regarding signals

Recommendation	*N*	Time until recommendation (days)		
		Mean	Median	Range
SmPC update	51	81	57	0–243
Routine pharmacovigilance	33	60	0	0–273
Referral started	9	54	27	0–186
DHPC	7	51	0	0–153
RMP update	7	132	144	0–234

Signals with ongoing evaluation were excluded; more than one recommendation per signal possible

DHPC dear healthcare professional communication, *PRAC* Pharmacovigilance Risk Assessment Committee, *Referral* a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines, *RMP* risk management plan, *SmPC* summary of product characteristics

The decisions to start a referral and to communicate a safety issue via direct healthcare professional communication took the least amount of time [54 days (median 27 days, range 0–186) and 51 days (median 0 days, range 0–153), respectively]. These results should be considered in the context of the fact that the PRAC conducts meetings on a monthly basis.

For 57 % of the signals, additional information was requested after the first discussion in the PRAC either from marketing authorization holders via a cumulative review ($n = 65$) or from member states, in the form of a non-urgent information request ($n = 8$). The cumulative reviews were submitted either within 30 or 60 days, or addressed during an ongoing PSUR procedure (see Fig. 3).

In the second part of the study, the hypothesis that drugs with signals are 'younger' (i.e., have been on the market more recently) on average than drugs without signals was tested. The comparison between drugs with signals ($n = 96$) and without ($n = 894$) at the end of the monitoring period showed that the drug age was significantly lower for drugs thath had identified safety issues in the period (median 12 vs. 20 years, $p = 0.01$, Mann–Whitney U test).

5 Discussion

At the time of approval, knowledge of the full benefit–risk profile of any new drug is incomplete owing to the well-known limitations of pre-approval research. Throughout a drug's life cycle, (serious) safety issues may emerge and while market approval may mark the end of drug development, it also marks the start of continuous evaluation of benefits and risks. The results of our study reaffirm the

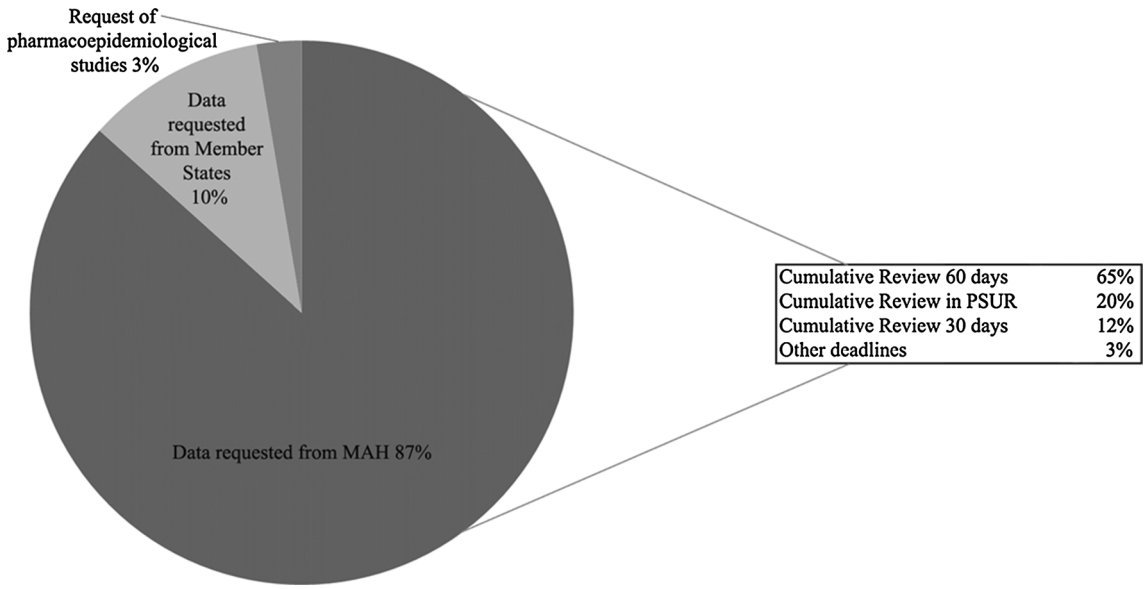

Fig. 3 Type of additional information requested during signal assessment at the PRAC. *MAH* marketing authorization holder, *PRAC* Pharmacovigilance Risk Assessment Committee, *PSUR* periodic safety update report

important role of spontaneous reporting in the detection of signals and the continuous need for monitoring because safety issues are also identified later in the life cycle of a drug.

The most frequent source of signals discussed by the PRAC were spontaneously reported adverse drug reactions (62 %). This is in line with studies from the USA [13], where spontaneous reports were also found to be the most frequent source. Ten percent of signals had multiple origins: spontaneous reports and literature, while another 6.4 % were identified exclusively from published case reports, which emphasizes the importance of continuously monitoring scientific publications [3, 14]. For a few signals arising from spontaneous reports, the evidence was based on one single case report (e.g., nomegestrol acetate-deep vein thrombosis, human papillomavirus vaccine-bronchospasm, and erlotinib-pancreatitis).

The drug age in our study was significantly lower for medicines with a signal as compared with those without (median 12 vs. 20 years, $p = 0.01$). Two papers regarding US Food and Drug Administration (FDA) safety-related drug label changes reported that the safety actions occurred at a median of 11 [15], and 10 years [16] after initial approval, similar to our results. Another paper investigating regulatory actions for biologicals reported the mean time to a safety-related regulatory action to be 3.7 years [17]. This shorter time is probably explained by the fact that this study only included biological drugs, which have an essentially different safety profile and are thus more intensively monitored post-marketing via post-authorization safety studies and/or registries.

While signals occur more frequently for younger drugs (see Fig. 2), safety issues still appear for drugs that have been on the market for more than 50 years (e.g., chloroquine, thiopental, codeine, and triamcinolone). This might be due to a change in the patterns of use for these drugs, better implementation of safety monitoring, increased awareness in relation to certain safety issues, as well as finalization of long-term observational studies. Such an example is the signal for codeine and life-threatening toxicity in cytochrome P450 2D6 ultra-rapid metabolizers, a safety issue that only occurs in a small sub-population [18].

Our study finding that a majority of the signals (60 %) were for drugs that have been on the market for at least 10 years highlights the need for continuous pharmacovigilance, as pointed out previously by Mol et al., who showed that some serious safety issues were communicated to healthcare professionals 10 or more years after approval [19]. Another contributing factor to the identification of signals for old drugs is that some signals are not new from a scientific point of view but they can appear to be so from a regulatory perspective (e.g., when a certain adverse reaction is listed in the summary of product characteristics in some countries but not in others).

The most frequent recommendation was a change in the product information and this is similar to what has been reported in relation to the post-marketing safety surveillance decisions taken in the USA [13, 20].

For the interpretation of the results, it is important to keep in mind that the signals discussed at the PRAC and hence considered in our study represent only a subset of all

signals discussed in the regulatory framework. Signals can be identified by various stakeholders. After assessment by member states, the need for discussion at the EU level is decided and signals are brought to the PRAC agenda. Signals can also be identified and dealt with in other regulatory procedures such as periodic reports or assessment of study results. As far as we are aware, there was no research that aimed to quantify and characterize signals managed in these alternative routes, and a comparison is not possible at this moment. Therefore, we cannot claim the generalizability of our results for signals handled outside the PRAC.

The decision to send a signal to the PRAC is currently not formalized in any documentation and is made on a case-by-case basis, considering both signal-related factors (seriousness of signal, public health impact, degree of exposure to the drug) as well as process-related factors (the fastest and most efficient route to implement a decision).

A time frame of 21 months from signal detection to action has been reported by Hochberg et al. [21] for the FDA system, although the data are not directly comparable, because there is a lag time between detection and first discussion at the PRAC and also between decision and actual implementation, which we did not take into account.

According to our analysis, the PRAC decision-making process seems efficient in the case of serious concerns leading either to referral or DHPC dissemination, which were handled more expeditiously than other decisions (see Table 2). This is in line with a recent study that described the PRAC activities since its initiation and reported some process indicators that showed that the system is more structured, faster, and with a more risk-proportionate approach [9].

A limitation of our work might be that only signals discussed at the PRAC were considered, although there are other regulatory pathways through which signals can be handled (e.g., PSURs) so we analyzed only a fraction of the available information. Limited availability and heterogeneity of exposure data precluded further analysis of this variable; therefore, we recommend increased standardization in its reporting, although we acknowledge the difficulties of acquiring accurately consistent exposure data at the EU level.

6 Conclusions

The objective of this study was to characterize the signals discussed at the EU level, since the PRAC started its activity. The importance of spontaneous reporting in signal detection and monitoring of safety issues throughout the entire life cycle of a medical product is confirmed by our study. We also found that the amount of time a drug has been on the market is correlated with the number of signals detected; however, further studies are necessary to find the adequate frequency of monitoring. The role of the new PRAC in improving signal prioritization and real-time signal management will be further clarified in its subsequent years of operation.

Acknowledgments No sources of funding were used to conduct this study or prepare this manuscript. Georgy Genov is the head of the Signal Management Section at the European Medicines Agency. Miriam Sturkenboom is heading a research group that conducts unconditional research on the safety and effects of drugs for several pharmaceutical companies (AstraZeneca, Pfizer, Eli Lilly), none of which is related to this current research. Alexandra Pacurariu, Preciosa Coloma, Anja van Haren, and Sabine Straus have no conflicts of interest that are directly relevant to the content of this study. The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the Dutch Medicines Agency or the European Medicines Agency or one of its committees or working parties.

References

1. Amery WK, ISPE. Why there is a need for pharmacovigilance. Pharmacoepidemiol Drug Saf. 1999;8:61–4.
2. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. PLoS Med. 2008;5:e67.
3. Stricker BHC, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ. 2004;329:44–7.
4. CIOMS Working Group. Practical aspects of signal detection in pharmacovigilance. Geneva; 2010.
5. EMA. Guideline on good pharmacovigilance practices, Module IX: signal management. 2012.
6. Commission Implementing Regulation (EU) No 520/2012. 2012.
7. Directive 2010/84/EU of the European Parliament and of the Council (Internet). (cited 2014 Apr 5). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN:PDF.
8. Countdown to July 2012: the establishment and functioning of the PRAC, EMA/315258/2012 (Internet). (cited 2014 Apr 15). http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/07/WC500129301.pdf.
9. Arlett P, Portier G, de Lisa R, Blake K, Wathion N, Dogne JM, Spooner A, Raine J, Rasi G. Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee. Nat Rev Drug Discov. 2014;13:395–7.
10. PRAC meeting minutes (Internet). (cited 2014 Apr 15). http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000353.jsp&mid=WC0b01ac05805a21cf.
11. PRAC recommendations on safety signals (Internet). (cited 2014 Apr 15). http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000375.jsp.
12. MedDRA. Introductory guide MedDRA version 15.1, MSSO-DI-6003-15.1.0. 2012.
13. Ishiguro C, Hall M, Neyarapally GA, Dal Pan G. Post-market drug safety evidence sources: an analysis of FDA drug safety communications. Pharmacoepidemiol Drug Saf. 2012;21:1134–6.
14. Pontes H, Clément M, Rollason V. Safety signal detection: the relevance of literature review. Drug Saf. 2014;37:471–9.

15. Moore TJ, Singh S, Furberg CD. The FDA and new safety warnings. Arch Intern Med. 2012;172:78–80.
16. Lester J, Neyarapally GA, Lipowski E, Graham CF, Hall M, Dal Pan G. Evaluation of FDA safety-related drug label changes in 2010. Pharmacoepidemiol Drug Saf. 2013;22:302–5.
17. Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HGM, Egberts ACG. Safety-related regulatory actions for biologicals approved in the United States and the European Union. JAMA. 2008;300:1887–96.
18. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med. 2009;361:827–8.
19. Mol PGM, Arnardottir AH, Motola D, Vrijlandt PJ, Duijnhoven RG, Haaijer-Ruskamp FM, et al. Post-approval safety issues with innovative drugs: a European cohort study. Drug Saf Int J Med Toxicol Drug Exp. 2013;36:1105–15.
20. Powers A, Cook G. Potential safety signals and their significance. Arch Intern Med. 2012;172:72–3.
21. Hochberg AM, Reisinger SJ, Pearson RK, O'Hara DJ, Hall K. Using data mining to predict safety actions from FDA adverse event reporting system data. Drug Inf J. 2007;41:633–43.
22. Edwards IR. Good pharmacovigilance practice and the curate's egg. Drug Saf Int J Med Toxicol Drug Exp. 2012;35:429–35.