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ORIGINAL RESEARCH



# New safety signals assessed by the Pharmacovigilance Risk Assessment Committee at EU level in 2014–2017

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**ABSTRACT**

**Background**: Safety monitoring of all drugs throughout their entire life cycle is mandatory in order to protect the public health. Our objective was to describe all new safety signals assessed at EU level by the Pharmacovigilance Risk Assessment Committee (PRAC).

**Methods**: Publicly available data on signals assessment from PRAC meeting minutes for the period January 2014–November 2017 were analyzed and classified.

**Results**: A total of 239 new signals for 194 drugs/drug combinations/therapeutic classes were evaluated by PRAC. A total of 154 signals were triggered by spontaneous reporting, 31 by literature case reports, and 26 by observational studies. In 188 signals, the drugs involved were authorized for more than 5 years. The drug classes for which most signals were detected were antineoplastic/immunomodulators ($n$ = 75), anti-infectives ($n$ = 34), and drugs acting on the nervous system ($n$ = 27). Signals were triggered for drug interactions ($n$ = 15), *in utero* exposure ($n$ = 7), medication errors ($n$ = 6), and for different disorders, among which the skin/subcutaneous tissue disorders were more common. PRAC recommendations consisted in label updates ($n$ = 86), in Direct Healthcare Professional Communications ($n$ = 17), and in eight recommendations for a more complex evaluation through referral procedures.

**Conclusions**: Most new signals assessed were triggered by spontaneous reporting and led to routine risk minimization measures, such as updating the product information.

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**KEYWORDS**
European Union; Pharmacovigilance Risk Assessment Committee; risk; safety signals; spontaneous reporting systems

## 1. Introduction

At the time of granting a marketing authorization (MA) for a medicinal product, the information evaluated by regulators for benefit–risk assessment relies on the totality of data collected from the ideal conditions of clinical trials, conditions that are limited mainly by the inclusion and exclusion criteria, sample size, and duration of these trials. Not all hazards are known at this point in time. With increased, highly variable prescription and utilization patterns in the post-marketing setting, new evidence on adverse drug reactions (ADRs) and therapeutic effectiveness (or lack thereof) will be collected. These evidences might ultimately lead to meaningful reassessments of a drug's benefit–risk profile. Several regulatory actions were taken in relation to the approach of pharmacovigilance activities in the recent years, due to important changes in the safety profile of different medicinal products, including the withdrawal of 19 products from the European Union (EU) market in between 2002 and 2011 [1,2].

For the last 10 years, ever since the first legislative proposal in December 2008 [3], meant to amend and strengthen the European legislation on pharmacovigilance, there was a gradual and sustainable shift toward a planned, proactive, and risk proportionate approach in pharmacovigilance. Pharmacovigilance activities are nowadays integrated into the life cycle of a product, these activities being planned before the product enters the EU market [4]. This approach was strengthened by a more recent amendment and rationalization of pharmacovigilance legislation, entering into force in July 2012, also aiming at providing a comprehensive overview of the pharmacovigilance system and all of its components [5–7].

At EU level, the Pharmacovigilance Risk Assessment Committee (PRAC) is responsible as of July 2012 for proactively assessing all aspects related to the risks of authorized medicinal products, including risk management planning and post-marketing benefit–risk assessments [8,9]. With the simplification of the ADR definition in EU, in order to capture all noxious and unintended effects of drugs, including medication errors, off-label use, overdose, misuse, and abuse, there was an increase in the pool of information captured through spontaneous reporting and other sources [1]. All this information is being captured in EudraVigilance, the EU database and system for recording and analyzing ADRs, and represents key data for safety signal detection. PRAC has the crucial role in the prioritization and scientific evaluation of such signals and making recommendations for management, including product

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information updates, new restrictions for use, and advice on optimal drug use [8].

In EU, a signal is defined as information arising from one or multiple sources, including observations and experiments, which suggest 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. [10].

New aspects of a known association may include changes in frequency, duration, severity, or outcome of the adverse event.

An important source of signals in drug safety is the spontaneous reporting system, which relies on ADRs reporting by health-care professionals and consumers, to national health authorities or pharmaceutical companies [11,12]. Signal detection and evaluation are essential elements of nowadays' pharmacovigilance, having been extensively studied during the last few years, throughout different European projects, in order to point pragmatic steps to improve signal detection practices [13,14,15]. It has the main goal of enabling a more rapid detection and confirmation of new ADRs and other drug-related problems, and of informing authorities about possible regulatory actions that should be taken for minimizing risks, most often a change in a product's prescribing information [12].

The objective of this study was to provide a descriptive overview of the safety signals evaluated by the PRAC during 2014–2017. This period was chosen as the signals evaluated by the PRAC in their first 18 months of operation within the European Medicines Agency (EMA), in between July 2012 and December 2013, were previously evaluated by another research team [12].

## 2. Methods

The information regarding safety signals was extracted from the PRAC meeting minutes, which are available for the public on the EMA website. All of the signals evaluated by PRAC in between January 2014 and November 2017 were included in the analysis. Only signals for which all variables of interest to be analyzed in this study were found in the minutes were included. Data regarding a drug's first authorization were taken from the European Union Reference Date, when not already provided in PRAC's meeting minutes.

Variables such as drug class (according to the Anatomical Therapeutic Chemical classification), type of MA of a drug, time since MA grant, the regulatory agency/EU Member State (MS) or other body detecting the signal, nationality of the rapporteur, type of the signal, as well as its source, the System Organ Class affected, and PRAC's final recommendations have been assessed in this study.

Medicinal products were categorized as being authorized through the centralized procedure (single MA across all EU countries), national procedures (the product is authorized at a national level in one or more MSs), or having been authorized through both procedures (i.e. signals evaluated as a class effect: the safety of dual blockade of the agents acting on the renin–angiotensin system, products which are authorized through both procedures). Signals' source was categorized in (1) spontaneous reporting systems, (2) literature case reports from literature monitoring, (3) randomized clinical trials, (4) observational studies, and (5) other sources. When the 'New signals detected from other sources' category was indicated in the PRAC meeting minutes, but a clear indication of the source was offered, the signal's source was accounted into one of the abovementioned categories (e.g. a cohort study categorized as observational study). Under the category 'other sources,' were considered signals detected from national health authorities' assessments and safety warnings, following type II variations, or from nonclinical data.

Once a signal is brought to the PRAC attention for discussion and evaluation, their recommendation might usually include any or a combination of the following: (1) no need for further evaluation or action at that point of time, (2) need for additional information (data submission request from a MS or from the MA holder [MAH], including requests for conducting a post-authorization safety study), (3) need for regulatory action. We categorized PRAC's final recommendations according to the action taken into (1) summary of product characteristics (SmPC) update, (2) patient information leaflet (PIL) update, (3) direct health-care professionals communication (DHPC), (4) update of the risk management plans (RMP), (5) start of a referral procedure, (6) routine pharmacovigilance (such as monitoring any relevant emerging information on the signal as it becomes available or addressing the signal in the next Periodic Safety Update Report [PSUR]), or (7) no regulatory action deemed necessary. One or several recommendations could have been issued for a signal. Signals for which a final PRAC decision was not available at the end of February 2018 have been labeled as still ongoing.

Descriptive statistics (counts and percentages) were used to characterize the variables assessed in this study.

No Institutional Ethical Committee approval was necessary as the study does not include human subjects, being an analysis of data from the public domain that is not covered by copyright, patent, or any other legal requirements for approval for use.

## 3. Results

In between January 2014 and November 2017, PRAC assessed 239 new signals for 194 drugs/drug combinations/therapeutic classes. The signals that were ongoing from before January 2014 were not included in the present analysis. Moreover, if a signal was initially detected for a drug and then extended to the whole therapeutic class, it was considered as a single signal. If a signal was detected from one source and after an initial assessment was kept under supervision as more data became available, being reconfirmed afterwards in other sources, it was also considered a single signal. The general characteristics of the signals evaluated by PRAC are presented in Table 1.

Almost half of the signals discussed have been detected by the EMA (44%). However, there are a few other notable MSs that have detected and reported many signals, such as The United Kingdom, Germany, France, The Netherlands, Spain, Denmark, Portugal, and Italy. There were also a few cases (four cases) where MAHs identified the signal and informed the PRAC (Figure 1).

Table 1. General characteristics of the signals evaluated by PRAC in between January 2014 and November 2017.

| | |
|---|---|
| Signals, *n* | 239 |
| Drugs/Drugs combinations/therapeutic classes, *n* | 194 |
| SOC affected by the signal[a], *n (%)* | |
| Skin and subcutaneous tissue disorders | 24 (10) |
| Blood and lymphatic system disorders | 14 (6) |
| Renal and urinary disorders | 15 (6) |
| Cardiac disorders | 12 (5) |
| Respiratory, thoracic, and mediastinal disorders | 12 (5) |
| Psychiatric disorders | 8 (3) |
| Immune system disorders | 7 (2) |
| Other | 150 (63) |
| Type of signal[b], *n* | |
| Drug interaction | 15 |
| *In utero* exposure | 7 |
| Medication error | 6 |
| Off-label use | 2 |
| Other | 209 |
| Signals' source[c], *n (%)* | |
| Spontaneous reporting systems | 154 (64) |
| Literature case reports | 31 (16) |
| Observational studies | 26 (11) |
| Randomized controlled trials | 10 (4) |
| Other | 49 (21) |

[a]A signal can be evaluated for more than one SOC affected.
[b]Most relevant presented in here.
[c]There were signals detected/verified in more than one source.
SOC: System Organ Class.

Sweden has been the country from which rapporteurs were most often appointed to take the lead over signals' evaluation, for a number of 40 signals (17%), followed closely by Germany, The United Kingdom, The Netherlands, Denmark, France, and Portugal.

Some of the discussed signals were related to drug interactions, *in utero* exposure, medication errors, and off-label use.

Signals have been detected for numerous System Organ Classes, prominently the following: skin and subcutaneous tissue disorders, blood and lymphatic system disorders, renal and urinary disorders, cardiac disorders, and respiratory, thoracic, and mediastinal disorders.

The vast majority of signals were triggered by spontaneous reporting (64%). Case reports from literature monitoring, observational studies, and less often randomized clinical trials also contributed to signal generation. Among other signal sources, the most notable were the safety warnings issued by health authorities from outside the EU (US Food and Drug Administration [FDA], Health Canada), cumulative safety reviews, and nonclinical data communicated by MAH and reviews/meta-analyses.

Out of all the drugs/drugs combinations/therapeutic classes discussed during PRAC meetings, 134 drugs have been authorized through the centralized procedure, 97 through national procedures, and 37 through both types of authorization (the last being included into the first two individual categories) (Table 2).

For almost 80% of the total number of signals assessed, the drugs have been authorized for more than 5 years (considering the time of signal evaluation). The median number of

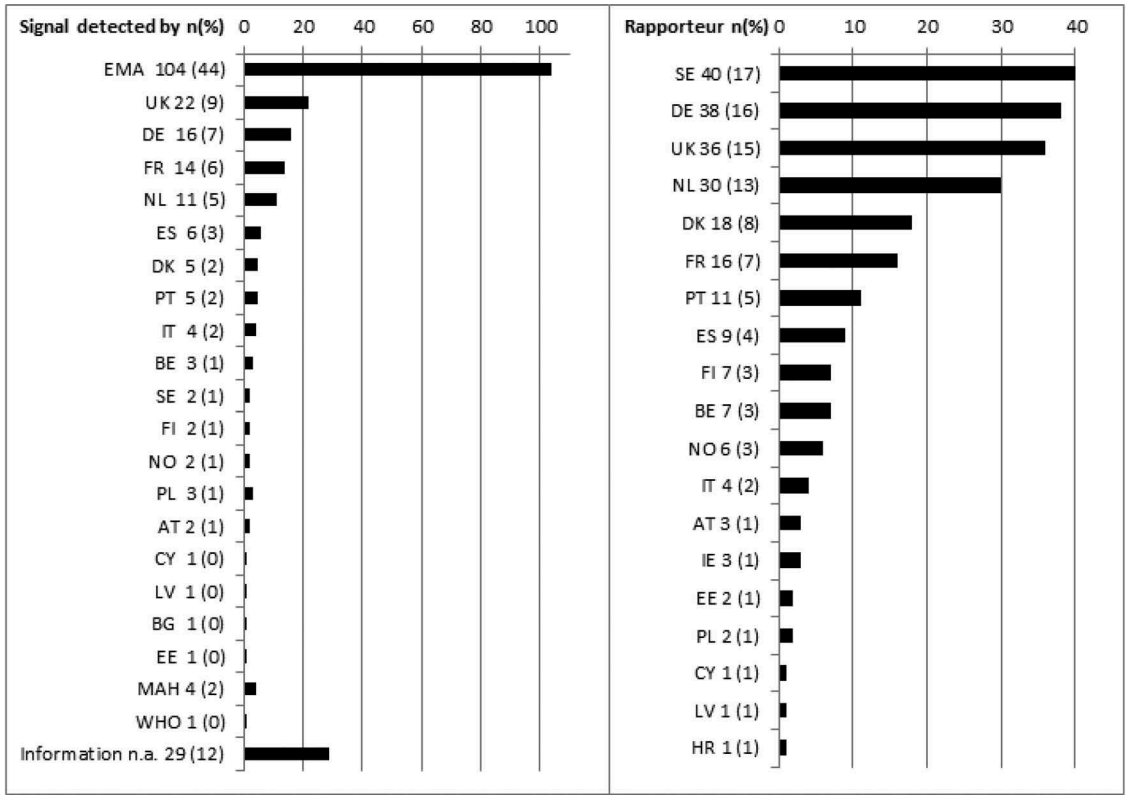


Figure 1. *left*: Regulatory agency/Member State detecting the signal, *n(%), right*: Country of origin of the PRAC rapporteur appointed for the signal management*, *n (%).*

EMA: European Medicines Agency; AT: Austria; BE: Belgium; BG: Bulgaria; CY: Cyprus; de: Germany; DK: Denmark; EE: Estonia; ES: Spain; FI: Finland; FR: France; HR: Croatia; IE: Ireland; IT: Italy; LV: Latvia; NL: Netherlands; NO: Norway; PL: Poland; PT: Portugal; SE: Sweden; UK: United Kingdom; MAH: marketing authorization holder; WHO: World Health Organization; n.a.: not available.*A signal can be evaluated by more than one rapporteur.

Table 2. Drugs for which signals were evaluated.

| | |
|---|---|
| Authorization procedure, *n* | |
| Authorized through CAP | 134 (69) |
| Authorized through NAP | 97 (50) |
| Mixed authorization[a] | 37 (19) |
| Time since marketing authorization, *n* (%) | |
| Authorized ≤5 years | 58 (24) |
| Authorized >5 years | 188 (79) |
| Both categories[a] | 7 (3) |
| Years since first authorization | 17 (0–85) |
| Drug class[b], *n* (%) | |
| Antineoplastic and immunomodulating agents | 75 (31) |
| Anti-infectives for systemic use | 34 (14) |
| Drugs acting on the nervous system | 27 (11) |
| Other | 106 (44) |

[a]When signal evaluated as a class effect, some of the individual drugs are falling under both categories (authorized through both procedures, and more and less than 5 years, respectively).
[b]Drug class counts are for each time the class was involved in a different signal.

years since first authorization to signal evaluation was 10.5 years (0–85), calculated for the drugs for which this information was available.

The drug classes for which most signals were detected and assessed were antineoplastic and immunomodulators, anti-infective drugs for systemic use, drugs acting on the nervous system. Although not as remarkable, signals were detected and assessed for the following classes as well: anticoagulants, fibrinolytics, antidiabetics, and hormones.

PRAC's first request in the signal evaluation process was for the MAH to submit a cumulative review of the signal in 60 days, and very rarely in 90 days. In most cases, after evaluating the review, PRAC would make their final recommendation. There were however cases, when the PRAC asked for further information to be submitted. In other cases, MAHs were requested to submit a cumulative review of the signal in their next PSUR, taking into account all the cases until the preestablished Data Lock Point.

PRAC's final recommendations most often consisted of variations to the marketing authorization, in the form of product information update (37%), including SmPC updates (*n* = 86, 37%) and when applicable PIL updates (*n* = 82, 35%). One or more SmPC sections were updated, among which the most frequently updated were undesirable effects (*n* = 63/86, 73.3%), special warnings and precautions for use (*n* = 54/86, 62.8%), interaction with other medicinal products (*n* = 7/86, 8.1%), posology and method of administration (*n* = 6/86, 7.0%), and contraindications (*n* = 3/86, 3.5%).

Sending a Direct Healthcare Professional Communication, which is considered an additional risk minimization measure, RMP updates and recommendations to start a broader safety evaluation through a referral procedure were also among PRAC's recommendations (Figure 2). There were a few cases in which no regulatory action was considered necessary. For other signals, PRAC's recommendation was for routine pharmacovigilance activities. Five signals were still ongoing at the time of this study.

## 4. Discussion

At the time of granting a new drug authorization for the market, the risk–benefit balance is judged as positive for a target population, in a specified indication. However, the full benefit–risk profile is not entirely characterized at this point. This is due, in general, to the well-known limitations of pre-approval research and the ideal conditions of randomized clinical trials which cannot reflect the different patterns of drug use in the post-authorization period. Throughout a drug's life cycle, ADRs that will vary in terms of severity, likelihood of occurrence, effect on individual and different categories of patients, and public health impact will be identified and characterized after approval [16,17]. Moreover, for innovative, first-in-class drugs, safety knowledge is often even less extensive at the time of approval, and new safety issues will be identified post-approval [18]. Signal detection is one important element in identifying new risks for all medicinal products. Although other sources like pre- and post-marketing factors [19,20] and social media [21] are being evaluated for their capacity to predict and detect safety signals, literature review and spontaneous reporting systems are still considered the starting point of the whole process of signal management [22].

Our study's findings are confirming the fact that spontaneous reporting remains an important source of safety alerts, as it represented the most frequent source of signals discussed by the PRAC throughout 2014–2017. Another study conducted on the signals evaluated by the PRAC in its first 18 months of activity, in between July 2012 and December 2013, on 125 signals, concerning 96 medicinal products, also

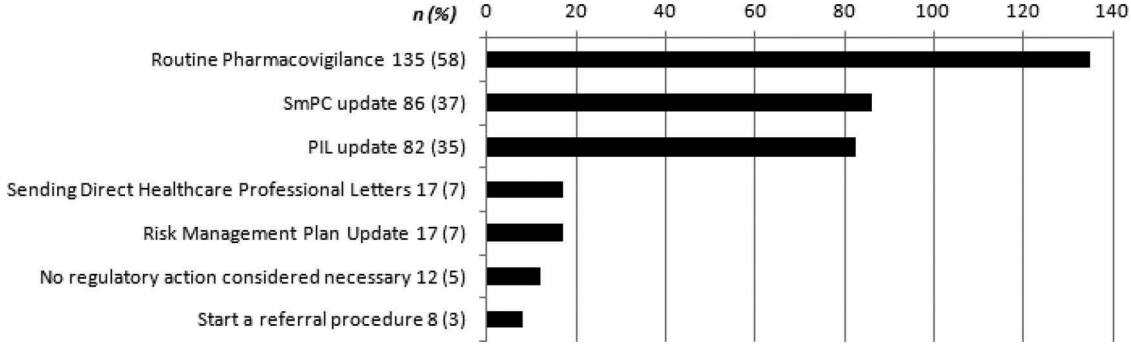


Figure 2. Pharmacovigilance Risk Assessment Committee's recommendations (five signals were still ongoing at the time of present data analysis; therefore, the percentage calculated is out of 234 signals for which PRAC issued a recommendation; there were signals for which PRAC issued more than one recommendation.).
SmPC: Summary of product characteristics update; PIL: patient information leaflet update.

revealed that the majority of signals were triggered by spontaneous reports (62%) [12], similar to our results (64%).

Almost half of the signals were detected by the EMA in the time frame evaluated. The efforts in signals management within the EU network are split between the EMA and the MS within a work-sharing process. For centrally authorized medicinal products, the EMA is responsible for EudraVigilance safety reports monitoring for signal detection. Half of the products in the time frame evaluated were centrally authorized – this explains why almost half of the signals were detected by the EMA. Lead MS are appointed to monitor data in EudraVigilance, to validate and confirm signals on behalf of the other MS, for active substances contained in medicinal products authorized nationally in more than one MS. Only validated signals by the EMA or MS are entered in the European Pharmacovigilance Issues Tracking Tool and will be brought to PRAC attention for further evaluation and recommendation for action. Therefore, only confirmed signals were evaluated.

The majority (80%) of the signals were for drugs that have been authorized for more than 5 years, with an average of 17 years until signal detection. This 5-year cutoff value was chosen as a new active substance is generally considered new, and subject to additional monitoring for quick identification of new safety information, in the first 5 years since market approval [23]. In The United States of America, there are recommendations for a rereview of the risk–benefit status of newly approved drugs at 5 years after approval [24]. The Pacurariu *et al*. study on PRAC signals also found that for 79% of the signals, the drug mean age (since authorization) was more than 5 years, very similar to our results, although the drug age was significantly lower for medicines with a signal as compared with those without (median 12 vs. 20 years, $p = 0.01$) [12]. The FDA detected post-marketing safety-related events at 10 years after market approval for 31% of all novel therapeutics approved in between 2001 and 2010 [16]. In Japan, safety-related regulatory actions after the launch of 338 new molecules in between 2004 and 2014 tended to occur sooner for molecules launched in the most recent years of the study versus those launched toward the beginning of the study period, this being closely connected with the accumulation of the data. The number of ADRs from spontaneous reports had positive correlations with the safety-related regulatory actions, spontaneous reporting representing in this study a cornerstone of post-marketing surveillance [25].

Our findings, which show that safety issues are still identified for old, well-established drugs (e.g. acenocoumarol, amiodarone, azathioprine/mercaptopurine, benzodiazepines, digoxin, methylprednisolone, paracetamol, valproate, among many others), might be due in part to the fact that safety monitoring and signal detection is much better regulated these days. Not only EU regulators but also MAHs as of November 2017 have the responsibility to monitor EudraVigilance data for signal detection and to determine any new risks or changes in already identified risks, and if these risks have an impact on the benefit–risk balance of the medicines authorized throughout EU [4]. Moreover, the fact that safety issues still appear for drugs that have been on the market for more than 30 years might be due to a change in the patterns of use for these drugs, which can lead to identification of new risks. Nevertheless, the fact that the majority of signals were identified for older drugs highlights the need for continuous, proactive pharmacovigilance for drug safety monitoring.

The most frequent PRAC recommendation for the 2014–2017 interval was a change in the product information. This is in line with PRAC recommendations from the previously analyzed period (2012–2013), when updating the SmPC was also the most common recommendation [12]. These results demonstrate the crucial role of PRAC in prioritizing and evaluating signals, ensuring that new or changed safety issues can be translated into product information updates for optimal, safe drug use. Similar decisions were also taken by the FDA as part of their post-marketing safety surveillance. In a 3-year time frame (2008–2010), label changes had occurred in 48% of the evaluated potential safety signals, the most common section adjusted being the 'Warnings and Precautions' section (62%) [26]. This was supported by another study that evaluated drug labeling changes proposed by FDA following safety issues in between 2010 and 2014, where the warnings (69%) and precautions (59%) sections were most often updated [27].

Communicating a safety issue through a Direct Healthcare Professional Communication that usually contains a recommendation on what specific action to take to minimize the risk was the next most common PRAC recommendation (in 7% of the signals from our study) after product information updates. This recommendation was usually accompanied by RMP updates. This is consistent with PRAC's previous recommendations when 6% of signals translated into such communications, and the decisions took the least amount of time (51 days) [12]. Communicating safety issues in a timely and appropriate manner is an important measure for promoting the rational, safe use of medicines, and preventing harm from adverse reactions. This method for safety communication was proved to be widely accessible as 88% of the National Competent Authorities from the EU publish DHPCs on their website [28]. It is however less clear how these communications on safety warnings impact the clinical practice [29].

For the most important safety issues, a referral procedure can be triggered when the interest of the Union is involved, and the EMA is then requested to conduct a scientific assessment of a particular medicine or a class of medicines. The safety-related referrals are also assessed by the PRAC. In the studied period, eight signals triggered a referral, comparing to the previous shorter period evaluated by Pacurariu *et al*. when nine referral procedures were started at PRAC's recommendation [12]. The referral procedures in our study were started for direct-acting antivirals indicated for hepatitis C treatment, ivabradine, testosterone, sofosbuvir, radium RA223 dichloride, canagliflozin and the whole sodium-glucose transport protein 2 inhibitors class involved in two different safety signals, and human coagulation (plasma-derived) factor VIII medicines.

## 5. Limitations

This study assessed only the signals discussed by the PRAC and not signals evaluated through other regulatory framework

and this could be regarded as a limitation. Moreover, in the present study, the time taken by the PRAC was not quantified to reach a decision, although in case of serious safety concerns, these were handled with priority. Patient exposure was also difficult to assess due to heterogeneity and limited information available.

## 6. Conclusion

This study highlights once again that spontaneous reporting remains an important source for signal detection in pharmacovigilance. PRAC's recommendations were in most of the cases for routine risk minimization measures such as updating the SmPC and PIL, and less often for additional risk minimization measures such as sending DHPCs or triggering a wider safety evaluation through referral procedures. The study showcases how important the PRAC's work has become within the EU pharmacovigilance system, for assessing all aspects related to signal management of all the products on the market.

## Key issues

- The spontaneous reporting system represents an important source for signal detection.
- Signals assessments most often led to updates of the product information as routine risk minimization measures.
- For more serious safety signals, additional risk minimization measures such as sending Direct Healthcare Professional Communications were taken or a broader safety evaluation through a referral procedure was initiated.
- The majority of signals (80%) were detected for drugs authorized more than 5 years, with a median age of 10.5 years at the moment of detection.

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## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

## Reviewer disclosures

A reviewer on this manuscript has disclosed that they are a member of the PRAC committee. This manuscript deals with PRAC. The authors could perhaps be members from EMA or the PRAC but nobody has spoken to this reviewer about this manuscript. Another reviewer on this manuscript has disclosed that they are one of the authors of a study discussed about in this manuscript.

## Author Contributions

AF, AM and CM were involved in the conception, design, analysis and interpretation of the data, and in the drafting of the paper; NBB and DL were involved in the analysis and interpretation of the data; all authors were involved in revising the paper critically for intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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