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Safety Signal Detection: The Relevance of Literature Review

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Abstract Adverse drug reactions (ADRs) represent an important risk for patients and have a significant economic impact on health systems. ADRs are the fifth most common cause of hospital death, with a burden estimated at 197,000 deaths per year in the EU. This has a societal cost of €79 billion per year. Because of this strong impact in public health, regulatory authorities (RAs) worldwide are implementing new pharmacovigilance legislation to promote and protect public health by reducing the burden of ADRs through the detection of safety signals. Although, traditionally, signal detection activities have mainly been performed based on spontaneous reporting from healthcare professionals and national health RAs, the new pharmacovigilance legislation underlines the relevance of other sources of information (such as scientific literature) for the evaluation of the benefit–risk balance of a certain product. This review aims to highlight the relevance of periodic scientific literature screening in the safety signal detection process. The authors present four practical examples where a safety signal that was detected from a literature report had an impact on the lifecycle of a drug. In addition, based on practical experience of the screening of medical and scientific literature for safety purposes, this article analyses the requirements of the new pharmacovigilance guidelines on literature screening and highlights the need for the implementation of a literature review procedure and the main challenges encountered when performing literature screening for safety aspects.

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Key Points

Several safety signals detected in literature reports have had a direct impact on the lifecycle of a drug

The reporting culture of healthcare professionals is usually less prevalent than the publishing culture

The wide difference in quality, accuracy, and completeness of scientific publications is one of the biggest challenges of literature search and review

1 Introduction

Health regulatory authorities (RAs) are intensifying safety regulations to boost the adoption of pharmacovigilance systems by biopharmaceutical companies [1].

The ultimate goal of the pharmacovigilance guidelines and regulations published by RAs is to establish that the marketing authorization holders (MAHs) ensure the evaluation of the benefit–risk profile of their medical product during its whole lifecycle. This is done by providing the RAs with individual case safety reports (ICSRs) involving their products, emerging safety issues that may lead to changes in the known benefit–risk balance of a medicinal product, and periodic reports of adverse drug reactions (ADRs) through a periodic benefit–risk evaluation report (PBRER) during the post-approval phase, where the MAH assesses the benefit–risk balance of their products in real-life situations [2].

The global information collected during the different pharmacovigilance activities will enable the determination of the product safety profile and the detection of new

effects not identified during the preapproval phase (signals). Furthermore, the large amount of safety data collected from everyday use of drugs will be effective in detecting even very rare reactions.

Although most safety signals originate from aggregated analysis of ICSRs reported by healthcare professionals to the RAs, relevant safety information can also be obtained from other sources, such as scientific reports focusing on retrospective analysis of hospital records from patients treated with a medicinal product (case–control, cohort studies, surveys, epidemiology databases). This kind of publication is crucial, for example, for the identification of new risk factors for drug toxicity among some specific populations (e.g., genetic polymorphisms, renal insufficiency, elderly, etc.). In addition, spontaneous reporting from healthcare providers requires a reporting culture that is usually less prevalent than the publishing culture. Healthcare providers are usually more interested in, and enthusiastic about, publishing their case reports in scientific journals than in reporting them to the RAs, mainly due to prestige and visibility within the scientific community. This makes literature searches a very important part of the surveillance of the state-of-the-art about a medicinal product, especially during its post-marketing phase.

The aim of this review is therefore to detail how periodic literature searches in the context of pharmacovigilance should be performed, to discuss the main difficulties when performing these searches, and to highlight the relevance of the literature review for the detection of safety signals.

2 Practical Examples

In this section, to highlight the relevance of literature screenings for safety monitoring, four practical examples will be presented, where a safety signal detected from a literature report had an impact on the lifecycle of a drug.

2.1 Example 1: Thalidomide-Induced Phocomelia (1961)

This first example of the relevance of literature publications for the detection of safety signals corresponds to the most emblematic example of pharmacovigilance.

With his famous letter published in 1961 in *The Lancet* about thalidomide-induced phocomelia, William G. McBride [3] brought to the attention of the medical world the link between the exposure to thalidomide during pregnancy and birth defects.

Thalidomide was first synthesized in 1953 and became popular as a sedative prescribed for the morning sickness often associated with pregnancy. However, in April 1961, obstetrician William McBride began to notice cases of a rare birth defect involving shortened or absent limbs in babies whose mothers had used thalidomide in pregnancy. The publication of his letter, mentioning a 20 % incidence of these birth defects, was the first report of this phenomenon since, at the time, there were no legal requirements to report ADRs to RAs. Thalidomide was thereafter withdrawn from the market because of this high risk of teratogenicity.

After the thalidomide scandal, healthcare providers became far more aware of the potential teratogenic effect of drugs and were more careful about the drugs they prescribed to pregnant women. One important development was the establishment of systems for post-market drug surveillance [4].

Thalidomide returned to market in 1998 for use in leprosy and multiple myeloma as an orphan drug. A registry of all patients prescribed thalidomide was maintained and a pregnancy-prevention program was provided for women receiving the drug.

2.2 Example 2: Granulocyte Macrophage Colony-Stimulating Factor and Increased Risk of Viral Replication (1998)

A systematic qualitative review of the literature was performed to assess the safety of granulocyte macrophage colony-stimulating factor (GM-CSF) in the treatment of neutropenia in AIDS patients (off-label use in the USA) [5]. At the time, some concerns had been raised about the safety of GM-CSF in AIDS patients in view of in vitro data available at that time suggesting HIV up-regulation by GM-CSF [6, 7]. This meta-analysis determined an increased risk of viral replication by the use of GM-CSF in AIDS patients that were not currently protected with antiretrovirals. This kind of safety concern would never have been detected by regular spontaneous reporting systems, as the relevant information came from in vitro studies published in the scientific literature.

2.3 Example 3: Nifedipine and Fatal Aplastic Anemia (1998)

During the 1990s, a variety of observational studies provided useful information regarding 'type A' ADRs (known as augmented reactions, which are dose dependent and predictable) of different drugs within a certain drug class (e.g., non-steroid anti-inflammatory drugs and gastrointestinal bleeding [8], selective serotonin reuptake inhibitors and upper gastrointestinal bleeding [9], third-generation oral contraceptives and venous thromboembolism [10–12]). During this period, other original articles passed unnoticed by the medical community and the RAs. One example is the case–control study linking six cases of fatal

aplastic anemia ('type B' ADR, known as bizarre or idiosyncratic reactions, which are dose independent and unpredictable) with the use of nifedipine [13, 14].

2.4 Example 4: Tamsulosin and 'Floppy Iris Syndrome' (2005)

The tendency for higher reporting rates of some ADRs can sometimes be explained by public and academic interest in the subject. One example is the ADR 'floppy iris syndrome' that was first described in the literature in April 2005 [15]. In this report, 15 cases were published for the drug tamsulosin but none were spontaneously reported to the RAs during the same period [16]. This underlies that ophthalmologists and surgeons seem to be more academically oriented, given their publication of this medically important event, rather than reporting it to the RAs. Nowadays, 'floppy iris syndrome' is listed in the summary of product characteristics, which seems to be most likely attributable to several literature reports of this ADR [16].

It is hoped that the effort of the RAs in clearly regulating the requirements for adverse event reporting will lead to further examples of literature-originated safety signals becoming scarcer every day.

3 Literature Search and Review as a Source of Safety Signals

The scientific literature is a significant source of efficacy, effectiveness, and safety information for the monitoring of the safety profile and of the benefit–risk balance of medicinal products, particularly in relation to the detection of ICSRs, new safety signals, or emerging safety issues [17].

Therefore, according to Module VI of the Guideline on Good Pharmacovigilance Practice (GVP) published by the European Medicines Agency (EMA) [18], the MAHs must implement a systematic approach to collect information about suspected ADRs from literature sources, which should be clearly documented and submitted to periodic quality control (QC) of a sample of retrieved references to determine the efficiency of this approach. This systematic approach should be defined in a standard operating procedure (SOP) that should detail all the activities performed for a literature search and how they should be documented. Namely, the MAH should keep track of the search construction, the databases used, the date of search, the results of the search (particularly in the event of zero results), the date of the review, the identification of the person who performed the search/review, the date of the QC, and the identification of the person who performed the QC [18, 19]. Records of the literature searches should be maintained in accordance with the regulatory requirements described in Article 12 of the Implementing Regulation No. 520/2012 on the performance of PV activities (as defined in Regulation No. 726/2004 and Directive 2001/83/EC from the European Parliament and European Council).

The MAH must conduct a systematic literature review of widely used reference databases (e.g. MEDLINE or Embase) as well as local journals in countries in which their medicinal products have a marketing authorization. This literature search should cover published scientific literature (e.g., full-text or abstract publications and information presented at scientific meetings, systematic reviews and meta-analyses, data from competitors, 'grey literature' [documents that are protected by intellectual property rights, but not controlled by commercial publishers, e.g. patents], dissertations and theses) and lay literature (e.g., newspapers, health magazines, internet sources) and should be performed at least once a week [18, 20].

During the literature search, the MAH should search for articles reporting ICSRs and articles containing safety-relevant information. The ICSRs published in the scientific literature are usually found in case report articles, case series, etc. The safety-relevant information can be retrieved in review articles, meta-analyses, observational studies, epidemiologic studies, etc. The latter are essential to detect ADRs not detectable with spontaneous reporting, such as adverse reactions that are frequent (and therefore neglected) in the population, or that have a long time interval between onset and manifestation of the reaction.

For the identification of a valid ICSR, the four criteria for a valid ICSR should be present (an identifiable patient; a suspected medicinal product; a suspected ADR; and an identifiable reporter who, for scientific publications, is the first author), and the product of the MAH should be registered in the country of the first author (except if the country of occurrence is specified in the article), irrespective of commercial status. If an ICSR is identified during the literature screening, it must be reported by the company (or designee) to the RAs in a similar way as spontaneous reports [20]. The MAH's responsibilities apply to reports related to medicinal products for which ownership cannot be excluded [18]. For MAH reporting according to the European legislation, if multiple medicinal products are mentioned in the publication, only those that are identified by the author(s) as having at least a possible causal relationship with the suspected ADR should be considered by the MAH [18]. However, when a product is registered in the USA, the establishment of the causality by the author is not required, as MAHs should collect and report any adverse event associated with the use of a drug, whether or not it is considered to be drug related [21].

For the purpose of safety signal detection, literature articles that present data analyses from publicly available

adverse event databases (such as the US FDA Adverse Event Reporting System [FAERS]) or that summarize results from post-authorization studies are particularly relevant. The main objective of those studies is to detect/evaluate specific risks that could affect the overall benefit–risk balance of a medicinal product [18]. New and significant safety findings (even if not serious) presented in these articles, which do not qualify as ICSRs, should be discussed in the relevant sections of the concerned PBRER and analyzed regarding their overall impact on the benefit–risk balance of the product.

It is expected that literature searching would start on submission of a marketing authorization application and continue while the authorization is active. It is the responsibility of the MAH to establish the most relevant source of published literature for each product (MEDLINE, Embase, congress abstracts, local journals). It is best practice to select one or more databases appropriate to a specific product. According to GVP, the title, citation, and abstract (if available) should always be retrieved and reviewed. All full texts for search results that are likely to be relevant to pharmacovigilance requirements should be obtained, as they may contain valid ICSRs or relevant safety information.

The MAH should collect all the ADRs suspected to be related to any of the active substances being part of a medicinal product independent of the strengths, pharmaceutical forms, routes of administration, presentations, authorized indications, or trade names of the medicinal product. In addition, if relevant and applicable, information on other active substances of the same class should be considered [18]. The risk evaluation should be based on all uses of the medicinal product, including use in unauthorized indications and use that is not in line with the product information.

If any new safety information that may have a significant impact on the benefit–risk balance of the product is found, it should be notified immediately as an emerging safety issue to the competent authorities in member states where the medicinal product is authorized [18].

Detailed guidance on the monitoring of the scientific and medical literature has been developed in accordance with Article 27(3) of Regulation (EC) No. 726/2004 and it is included in the Appendix 2 of the GVP Module VI.

For a variety of reasons, the MAH may decide to outsource the literature search services to another party [20]. However, it is important to notice that, regardless of the type of pharmacovigilance service provider, contractor, or consultant used, the MAH retains overall responsibility for the safety of its products, including the performance of the search and subsequent reporting. In the case of outsourcing, the SOP is usually replaced or supplemented by the literature review procedure (LRP). This procedure should include the same requirements of the literature review SOP as well as the distribution of responsibilities, timelines, training, and key performance indicators (KPIs) to determine whether the service provided by the contract research organization (CRO) meets the needs and obligations of the MAH. In addition, it is essential that there is comprehensive and detailed contractual documentation specifying which party carries out each of the various pharmacovigilance activities [20].

Overall, the MAH (or CROs contracted for outsourced activities) should implement a quality management system to ensure compliance with the necessary quality standards at every stage of their activities and to correct and improve the structures and processes where necessary [22].

4 Main Challenges of Literature Search and Review

Common issues may be encountered during the review of scientific publications for safety assessment:

- Reports vary widely in quality, accuracy, and completeness (details about the route of administration, the formulation, or the proprietary name of the suspected drug, the event outcome, the seriousness, and concomitant medication are often missing [23]).
- Each report represents the suspicion, opinion, or observation of the individual reporter, i.e. they are rarely proven associations.
- Significant under-reporting.
- Population exposure data is often unavailable.
- Patients are frequently not identifiable, or the case history is not clearly reported for each patient (e.g. 74 patients, 30 % of them female; 42 % presented rash and 47 % presented cough).
- ADRs may result from non-compliance of patient, medication error, or other factors.
- ADRs may be confounded with symptoms of the underlying disease.
- Notoriety bias (media attention to some adverse 'hot topics' can be responsible for some disproportionality in reports [23]).

Besides these issues inherent to the articles that are published and that cannot be influenced by the search criteria, other factors of a literature search for signal detection can be optimized to obtain the best result from the search performed:

- Choice of the source databases and search engines
- Choice of the search construction and search terms
- Use of search limits
- Defined review criteria

Decisions about the database selection, approach to record retrieval, term or text selection, and the application of limits need to be relevant to the purpose of the search.

4.1 Choice of the Source Databases and Search Engines

A variety of literature databases are available and present several differences:

- Accessibility—most of the databases are not free.
- Coverage—some databases are more specialized in a certain type of publication. A systematic review that compared hand-searching (as gold-standard) with the results of searching electronic databases to identify reports of randomized controlled trials (RCTs), showed that only 55 % of the RCTs were retrieved in MEDLINE and 49 % in Embase [24].
- Overlap—the overlap of the journals available in the different databases is incomplete:
- Of 4,800 journals indexed in EMBASE, 1,800 are not indexed in MEDLINE.
- Of 5,200 journals indexed in MEDLINE, 1,800 are not indexed in Embase [25].

Due to these differences, none of the available databases offers a complete sensitivity for the literature screening. Therefore, the periodic literature search should be performed in various carefully selected databases. The characteristics of the most widely used databases are summarized in Table 1.

4.2 Choice of the Search Construction and Search Terms

When defining the appropriate search string, the two different properties of the search criteria should be balanced:

- Recall (or sensitivity)—proportion of records retrieved when considering the total number of relevant records that are present in the database.
- Precision (or specificity)—proportion of 'hits' that are relevant when considering the number of records that are retrieved.

Good search construction should result in an output with low recall and high precision. The highest recall will be achieved by searching only the medicinal product name and active substance name (in all their variants). Usually, other terms are added to the search to increase precision.

In cases of an extremely high number of 'hits', the MAH may prepare two different search constructions to be run in parallel every week: one for the purpose of ICSR detection and another for the purpose of signal detection.

For the purpose of ICSR detection, the search string can exclude records for pharmaceutical forms or routes of administration not approved for that MAH. The literature search should be performed to find records for active substances (and excipients or adjuvants that may have a pharmacological effect) and not for brand names only. The search should include possible different spellings, alternative names, number or codes for newly developed products, chemical names, and active metabolites.

For the purpose of signal detection, the search should not exclude special types of reports that need to be addressed in PBRERs (e.g., reports of asymptomatic overdose, other routes of administration, medication error, off-label use, misuse, abuse, occupational exposure, uneventful pregnancy, use in pediatric population, etc.) [17]. Records of unbranded products or records from other company brands should not be routinely excluded.

4.3 Use of Search Limits

If limits are applied to the search criteria, they should be relevant to the purpose of the search (limits to the publication language are generally not acceptable).

Limits can be applied to produce results for date ranges. Care should be taken to ensure that the search is inclusive for an entire time period (e.g., records that may have been added later in the day for the day of the search should be covered in the next search period). The search should also retrieve all records added in that period, and not just those initially entered or published during the specified period (ensuring that records that have been updated or retrospectively added are retrieved).

The use of publication type limits is not robust for the detection of ICSRs, because an ICSR might be presented within review articles or study publications that are not usually indexed as 'case reports'.

As an example of the effect of the search criteria and search limits on the obtained output, we simulated a search performed in PubMed for the originator MAH of omeprazole (Astra Zeneca) to retrieve the reports regarding omeprazole (brand name: Losec®) published in 2008, with special interest in the reports of hypomagnesemia [26]. According to the different options of the search string, the output has different recall and precisions as can be seen from the examples presented in Table 2.

4.4 Defined Review Criteria

The review criteria concerning the assessment of literature publications for the detection of ICSRs are clearly defined and detailed in the regulatory documents. However, the review criteria defined for the detection of safety-relevant information are very broad and allow for subjective interpretation depending on the MAH.

In fact, every MAH will have to define what is considered 'unknown'. The MAH may decide to refer only to their reference safety information (RSI) to define what is known or not for their products. However, this approach

Table 1 Relevant medical databases and search engines for periodic literature screening

	Host	Content	Advantages	Disadvantages
Medical databases				
MEDLINE	US NLM of the NIH	Journal citations and abstracts for biomedical literature in more than 5,000 biomedical journals	Worldwide coverage; can be accessed free of charge through PubMed	Insufficient coverage
Embase (http://www.embase.com/home)	Elsevier	Over 24 million indexed records and more than 7,600 currently indexed peer-reviewed journals from 1947 to the present	Highly versatile; multipurpose; up to date; has its own search engine; allows for simultaneous search in MEDLINE and Embase databases; includes over 5 million records not covered in MEDLINE; in-depth indexing of drug-related and clinical literature, with a particular focus on comprehensive indexing of ADRs	Access costs
Cochrane Library (http://www.cochrane.org)	John Wiley & Sons, Ltd	Groups several databases mainly oriented for clinical reports: Cochrane Database of Systematic Reviews (compiles systematic reviews of primary research in human health care and health policy); DARE (non-Cochrane reviews); CENTRAL—includes 530,000 citations for RCTs; Cochrane Methodology Register; HTA database; NHS EED	Highest standard in evidence-based healthcare	Access costs
CINAHL (http://www.ebscohost.com/)	EBSCO	Provides full text for hundreds of nursing and related health journals indexed in the CINAHL database and additional materials with concise overviews of diseases and conditions and outlines of the most effective treatment options	More oriented towards journals focusing on nursing, paramedics, ergotherapy, and psychology	Access costs
Search engines				
PubMed (http://www.ncbi.nlm.nih.gov/pubmed/)	NCBI	Journal citations and abstracts for biomedical literature in more than 5,000 biomedical journals	Free of charge; search engine for MEDLINE	Insufficient coverage
Ovid (http://www.ovid.com)	Wolters Kluwer	4,500 e-books and book collections, over 1,300 premium, peer-reviewed journals, dozens of journal collections and over 100 bibliographic and full-text databases	Another search interface to MEDLINE; search filters are similar to PubMed, but uses slightly different search syntaxes	Access cost
ISI Web of Knowledge and ISI Web of Science (http://apps.webofknowledge.com/)	Thomson Reuters	ISI Web of knowledge is a multidisciplinary database including references from the basic sciences and the social sciences ISI Web of Science is a search engine focused on basic science that runs on a database containing more than 10,000 science journals and more than 110,000 conference abstracts	High coverage	Complex search engines; access costs

Table 1 continued

	Host	Content	Advantages	Disadvantages
Scopus (http://www.scopus.com)	Elsevier	Abstract and citation database of research literature and web sources covering over 20,500 titles from more than 5,000 publishers worldwide. Contains 49 million records, 78 % with abstracts, includes over 5.3 million conference papers, and provides 100 % MEDLINE coverage	High coverage	Access costs
Google Scholar (http://scholar.google.com/)	Google	Information across many disciplines and sources: articles, theses, books, abstracts, and court opinions, from academic publishers, professional societies, online repositories, universities, and other websites	Free of charge; useful for a quick initial search and for the search of conference abstracts	Real coverage is unknown; can be spamed; complex search algorithm combining the frequency of keywords and the number of times an article is cited by others (highly cited references will appear in the beginning of the output, which can be a source of bias)

ADR adverse drug reaction, *CENTRAL* Central Register of Controlled Trials, *DARE* Database of Abstracts of Reviews of Effects, *EED* Economic Evaluation Database, *HTA* health technology assessment, *NCBI* National Center for Biotechnology Information, *NIH* National Institute of Health, *NLM* National Library of Medicine, *RCT* randomized clinical trial

has important limitations if the RSIs are out of date. In this case, the MAH may decide to use other sources to evaluate if an adverse event is known for that particular medicinal product, but this choice may also compromise the objectivity of the final assessment of the literature outputs.

This ambiguity is particularly evident in cases of special situations such as the following:

- Pregnancy and breastfeeding—according to the GVP module VI, pregnancy reports without information on congenital malformation, without outcome data, or reports that have a normal outcome should not be reported to RAs but should be collected and discussed in the PBRERs. Importantly, a signal of a possible teratogen effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to the RAs. Exposure to a medicinal product from breast milk should only be reported to the RAs if associated with ADRs.
- Pediatric and elderly population and other subpopulations—due to the scarce availability of clinical trials regarding these particular populations, all the information gathered in the context of pharmacovigilance is extremely important, especially regarding population-specific ADRs or risk factors.
- Overdose, abuse, off-label use, misuse, medication error, use on an unauthorized population, or occupational exposure—if this kind of report is not associated with an ADR, they should not be reported to the RAs; however, they should be considered for the PBRER. When those reports constitute safety issues impacting on the benefit–risk balance of the medicinal product, they should be notified to the RAs.
- Lack of efficacy—reports of lack of efficacy generally do not have reporting requirements but they should be discussed in the PBRER.

Finally, the subjectivity of the reviewer performing the literature screening should be minimized by the preparation of clear working instructions that should define in detail the approach that should be undertaken for each particular situation and by adequate training of all staff involved.

5 Discussion/Conclusion

Clinical trials performed with the aim of drug approval by RAs usually involve patient populations, the sample size of which is usually too small to detect the occurrence of infrequent ADRs [5]. The collection and assessment of post-marketing ADRs allows for the assessment of a more diverse population (diverse by disease, age, gender, race, concomitant medications, and comorbidities) than primary pre-marketing studies [5]. The conditions in which drugs

Table 2 Practical example of the relevance of search limits in literature screening

Search string	References retrieved	Recall	Precision	Observations
(((Omeprazole AND Losec))) AND ("2008/01/01" [Date - Create] : "2008/12/31"[Date - Create])	2	↓	↑	All information regarding competitors or therapeutic class is missed
(((Omeprazole OR Losec))) AND ("2008/01/01" [Date - Create] : "2008/12/31"[Date - Create])	303	↑	↓	Most complete search strategy
(((Omeprazole OR Losec))) AND ("2008/01/01" [Date - Create] : "2008/12/31"[Date - Create]) AND (case report OR ICSR[Publication Type])	39	↓	↑	ICSRs reported inside other types of articles will be missed
(((Omeprazole OR Losec))) AND ("2008/01/01" [Date - Create] : "2008/12/31"[Date - Create]) AND adverse reaction	4	↓↓	↑	Special types of reports not associated with ADRs will be missed[a]
(((Omeprazole OR Losec))) AND ("2008/01/01" [Date - Create] : "2008/12/31"[Date - Create]) AND hypomagnesaemia	1	↓↓	↑	Search criteria too restrictive; specific ADRs should never be included in the search criteria

ADR adverse drug reaction, *ICSR* individual case safety report

[a] With this search string, a known relevant reference from Shabajee and collaborators focusing on omeprazole and hypomagnesaemia is missing [26]

are used in the post-marketing phase are also more diverse, with different doses and routes of administration, different durations of use, use for unapproved ('off label') indications, and possible useful or harmful drug interactions [5]. The use in real-life situations can reveal some adverse events that may not be recognized as drug related if not previously observed in approved, labeled indications.

The diversified real-life scenarios of drug use associated with the under-reporting of adverse events in the post-marketing phase causes delays in the identification of drug-related safety problems. This is where the scientific literature (including the systematic reviews and meta-analysis of the published literature) shows its relevance for the detection and quantification of the incidence of rare but important adverse events, as they could be confirmed by the few examples presented above.

There are also other published examples of known safety issues that are not retrospectively identified by data-mining methods using pre-defined thresholds [1], which suggests that some healthcare professionals, especially in the academic sector, are more prone to publish than to report. Case reports derived from literature can have a significant clinical impact, especially for rare events that might not be detected in preapproval clinical studies [27].

In 2013, Klose et al. [16] conducted, in cooperation with the German Medicines Manufacturers Association, an analysis examining more than 25,100 spontaneous and literature cases that occurred between 2007 and 2008. This article is the first systematic analysis of ICSRs compared with literature cases. According to their analysis, data derived from the two reporting systems seem to be valid and robust. However, none of the two systems could be used as a standalone system. The combination of both is necessary for an adequate assessment of a drug's safety, given that for one drug an unexpected adverse event might be detected (earlier) with regular literature screening, whereas for another drug an early signal might be detected via the spontaneous reporting system. The results of this publication also indicate that regular literature screening seems to be of special importance for newly marketed drugs, for approval of new indications or new populations (e.g. elderly, children) as seen for tamsulosin (i.e., floppy iris syndrome).

Therefore, initiatives like that of the EMA to publish regulations regarding the process that should be put in place to perform an adequate literature screening for safety purposes should be followed and implemented by other national non-EU RAs. This will reinforce the valuable role of the safety information published in the scientific literature on the post-marketing assessment of the benefit–risk balance of medicinal products and thus contribute to more rational and safe use of medicines, i.e. the right drug prescribed to the right patient at the right time.

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