When More Is Less: An Exploratory Study of the Precautionary Reporting Bias and Its Impact on Safety Signal Detection

Kevin Klein[1,2], Joep H.G. Scholl[3], Marie L. De Bruin[1,4], Eugène P. van Puijenbroek[3,5], Hubert G.M. Leufkens[1] and Pieter Stolk[1,2]

Concerns have been expressed that large numbers of nonvalue-added reports have been accumulating in adverse drug reaction (ADR) databases, for example, via patient support programs. We performed an assessment of the impact of such reports, which we refer to as "precautionary reports," on safety signal detection in the Netherlands. The case narratives of ADR reports of three case products were screened with text-mining algorithms to identify those reports that lack a causal relationship with the suspected medicinal product. We demonstrate that precautionary reports impede the optimal use of the pharmacovigilance system by, on the one hand, masking safety signals and, on the other hand, creating spurious signals. The precautionary reporting bias and its suppressing effect on statistical signal detection results in an altered adverse event safety profile. The findings from this study highlight the need for a better alignment between regulatory authorities and marketing authorization holders regarding pharmacovigilance guidelines.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Concerns have been expressed that large numbers of potentially nonvalue-added reports have been accumulating in ADR databases; for example, as a result of the extensive patient contact by MAHs in patient support programs. Currently, limited information about such nonvalue-added reports and their actual impact on statistical signal detection is available.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The objective of this study was to explore the impact of such reports, which we refer to as "precautionary reports," on safety signal detection in ADR databases.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ This study demonstrated for the first time the existence of the precautionary reporting bias and its suppressing effect on statistical signal detection, by masking safety signals and creating spurious signals, resulting in an altered adverse event safety profile.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ This study highlights the need for a better alignment between regulators and MAHs as to what reports need to be submitted to regulatory authorities.

The reporting of an adverse drug reaction (ADR) by healthcare professionals or patients plays a key role in the postmarketing surveillance of medicinal products in the European Union (EU). ADRs can be reported directly to national pharmacovigilance centers (NPCs) or to the marketing authorization holder (MAH) of the suspected medicinal product.[1–4] Whereas NPCs mostly receive spontaneous reports, which are voluntary reports from healthcare professionals and increasingly from patients themselves, that describe an ADR, MAHs also receive solicited ADR reports, e.g., from organized data collection systems, such as patient support programs (PSPs), noninterventional studies, or compassionate use programs.[5] ADR reports collected by NPCs and MAHs are both submitted to the EudraVigilance Post-Authorisation Module (EVPM), the European ADR database that is managed by the European Medicines Agency (EMA). ADR data can be exchanged through EudraVigilance with NPCs to complement national ADR databases with ADR reports received by MAHs in the respective Member State.[5,6]

Statistical signal detection based on disproportionality methods are frequently applied to European and national ADR databases to detect safety signals for medicinal products. These automated methods screen ADR databases for signals of disproportionate reporting (SDRs), which indicate any adverse event for a medicinal product that is disproportionately highly represented.[7,8] In

[1]Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands; [2]Exon Consultancy, Amsterdam, The Netherlands; [3]The Netherlands Pharmacovigilance Centre Lareb, The Netherlands; [4]Copenhagen Centre for Regulatory Science (CORS) at the Department of Pharmacy, University of Copenhagen, Copenhagen, Denmark; [5]PharmacoTherapy, -Epidemiology and -Economics – Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands. Correspondence: K. Klein (k.klein1@uu.nl)

Received 14 June 2017; accepted 7 September 2017; advance online publication 25 October 2017. doi:10.1002/cpt.879

the ADR database of the Netherlands Pharmacovigilance Centre Lareb, the reporting odds ratio (ROR) is the standard method for detecting SDRs. This statistical measure is part of the method used to screen the complete ADR database (combining spontaneous and solicited reports), to identify SDRs that exceed a predefined threshold, which are then considered for further assessment and evaluation.[9]

Various studies have highlighted the existence of *competition biases* that may decrease the performance of statistical signal detection methods applied to ADR databases to detect safety signals. For example, Pariente *et al*. presented a "signal competition bias," where the event of interest is significantly associated with other medicinal products, thus increasing the background-reporting rate, and hence the threshold for the medicinal product of interest to create an SDR.[10,11] The subsequent reduction in SDR detection is referred to as the *masking effect*.[12,13] The same masking effect was also identified for a different type of competition bias reported by Hauben and Hochberg[14] and later described as the "event competition bias" by Salvo *et al.,* where the reporting of a large number of (often well-known) events for a given medicinal product may mask (previously unknown) associations of the same medicinal product with other events.[15]

In this study we investigated the existence of another form of competition bias that could lead to the masking of SDRs. Some concerns have been expressed that the extensive patient contact by MAHs through organized data collection systems (in particular, PSPs) leads to the elevated reporting of (often unrelated) events.[16,17] One example of this type of reporting is the disproportionate reporting of patient deaths found in the US Food and Drug Administration's Adverse Event Reporting System (FAERS). These reports of patient deaths often concerned terminally ill patients enrolled in PSPs, for which the causality with the product was not confirmed.[16,18] It has been pointed out that these reports are characterized by poor documentation of the medical context.[16] The rationale behind this reporting is not fully explained, but suggests a potential implication of the current pharmacovigilance requirements for MAHs. Current guidelines state that if the causal relationship between an event and the medicinal product cannot be ruled out, it should be considered an ADR. The nature of these guidelines implies that the biological plausibility as to whether the event is caused by the product is irrelevant.[19] Therefore, these guidelines oblige MAHs to also submit reports of (potentially unrelated) events for which the causal relationship cannot be ruled out (e.g., due to the limited information that is available), as these events still meet the regulatory definition of an ADR.

These reports could be regarded as "precautionary reports" by MAHs to meet the regulatory requirements. It was argued that these precautionary reports, when submitted to ADR databases, could create spurious signals.[16] However, and more important, by increasing the background-reporting rate for the medicinal product of interest, these precautionary reports could increase the threshold for SDRs to be detected, thus potentially masking interesting (yet undetected) safety signals. Currently, limited information about such precautionary reports and their actual impact on statistical signal detection is available.

Therefore, the objective of this study was to explore the effects of precautionary reports on the performance of statistical signal detection methods and the potential masking of safety signals with three real-world case studies in the Dutch ADR database.

RESULTS

Of the 157,833 reports collected in the Dutch ADR database since the start of data collection, 3,112, 2,555, and 689 reports were related to the erythropoietin (case product I), the bisphosphonate (case product II), and the endothelin receptor antagonist (case product III), respectively. These reports relate to 4,327, 6,531, and 1,555 medicinal product/event associations, respectively.

The assessment of the case narratives resulted in the identification of 2,757 (89%) precautionary reports for the erythropoietin, 2,023 (79%) for the bisphosphonate, and 409 (59%) for the endothelin receptor antagonist. These reports relate to 3,591 (83%), 4,922 (75%), and 716 (46%) medicinal product/event associations for the three respective case products. Furthermore, the assessment of the case narratives revealed that 59%, 98%, and 27% of the precautionary reports for the erythropoietin, bisphosphonate, and the endothelin receptor antagonist, respectively, were clearly attributable to organized data collection systems. A respective 81%, 51%, and 83% of the precautionary reports relate to spontaneous reports (**Figure 1**).

An overview of the five most reported events based on the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) for the reports classified as precautionary reports for each case product is provided in **Table 1**. The event "death" was the most reported event in precautionary reports for all three case products, e.g., 36% of all medical product/event associations reported for the erythropoietin case are related to the event "death." Looking at all reports with the event "death" for the erythropoietin, the bisphosphonate, and the endothelin receptor antagonist, our algorithm classified 99%, 95%, and 84% of the reports as precautionary reports, respectively (**Table 1**). Other events from the top 5 are also highly associated with precautionary reports.

Initially, a total of 45, 175, and 64 SDRs were detected (based on the ROR) for the erythropoietin, the bisphosphonate, and the endothelin receptor antagonist, respectively (**Table 2**, **Figure 2**).

After the exclusion of the precautionary reports from the ADR database, 16 new SDRs were detected for the erythropoietin, 8 for the bisphosphonate, and 5 for the endothelin receptor antagonist. Of these *unmasked* SDRs, 10 (63%), 7 (88%), and 4 (80%) SDRs, respectively, are considered safety signals requiring further evaluation due to the absence of obvious confounders, i.e., these SDRs are not related to events associated with the natural course of underlying disease, the indication, (mis-) use, or a patient outcome (**Table 3**).

For all three case products, the exclusion of precautionary reports from the ADR database also resulted in SDRs that were no longer appearing. For the erythropoietin, bisphosphonate, and the endothelin receptor antagonist, 27, 101, and 26 SDRs, respectively, were not detected anymore after exclusion of the precautionary reports from the ADR database (**Table 2**, **Figure 2**).

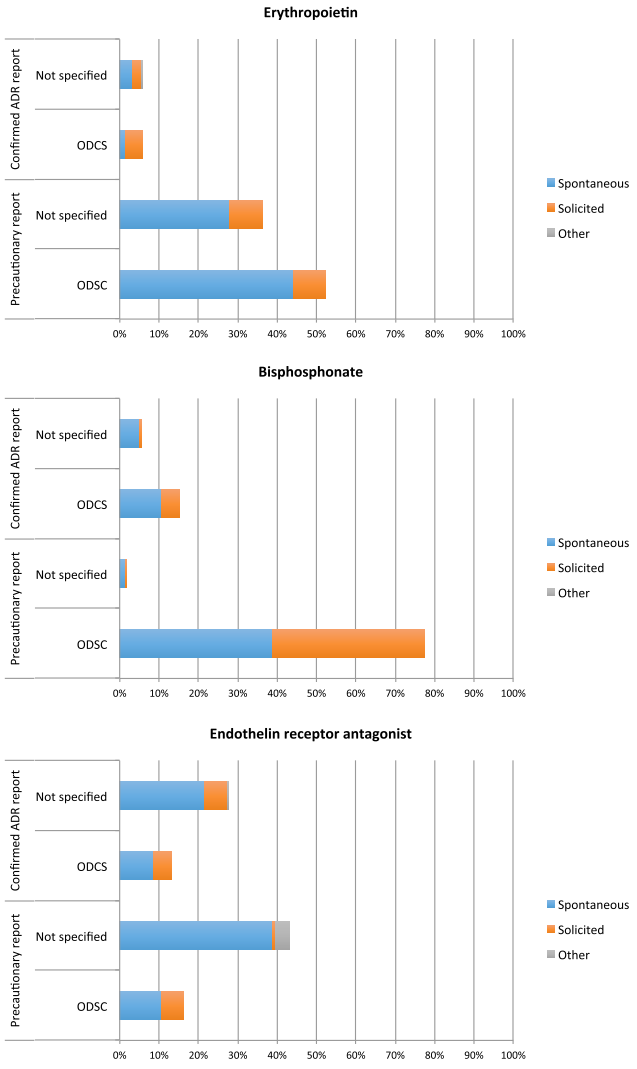

Figure 1 An overview of the reports for the erythropoietin (n = 3,112), the bisphosphonate (n = 2,555), and the endothelin receptor antagonist (n = 689), as a percentage of the total reports stratified by report source and report type. Report source: whether an ODCS was identified; report type: spontaneous, solicited, or other (if unclear); ODCS: organized data collection system. [Color figure can be viewed at cpt-journal.com]

DISCUSSION

The results from this study demonstrate for the first time the existence, and quantify the impact of, precautionary reports on statistical signal detection methods. The type of competition bias described in this article is hereafter referred to as the "precautionary reporting bias." The exclusion of the large number of identified precautionary reports from the ADR database resulted in the unmasking of previously undetected SDRs. Moreover, the existence of precautionary reports in ADR databases can trigger the detection of spurious signals: SDRs that are generated by precautionary reports and do not appear any more after the exclusion of the precautionary reports from the database. The exclusion of precautionary reports from the database thus improved the quality of signal detection. Both effects result in an altered *adverse event safety profile* for all three cases, which signifies the public health relevance of this bias.

For the erythropoietin and bisphosphonate cases, we identified that most of the precautionary reports were clearly attributable to organized data collection systems, all relating to PSPs (**Figure 1**). For the endothelin receptor antagonist, 27% of the precautionary reports were attributable to organized data collection systems, the majority relating to noninterventional studies in particular. For the erythropoietin and the endothelin receptor antagonist, however, we believe that the identification of organized data collection systems in precautionary reports is an underestimation, as for most of these reports the report source was not clearly identifiable.

Precautionary reports negatively impact the performance of statistical signal detection based on disproportionality methods in two ways. First, precautionary reports increase the chance of the detection of false-positive signals (Type I errors), which we refer to as spurious signals. Second, precautionary reports increase the chance of not detecting signals that otherwise would have been detected, so-called false-negative signals (Type II errors), which is also described by the *masking effect*. Both Type I and Type II errors can be explained with the two-by-two contingency table (**Box 1**), whereby the C and D quadrants remain constant. The presence of precautionary reports for a medicinal product of interest increases the background-reporting rate represented by the denominator (B) and thus the threshold for the event of interest (A) to be detected. In parallel, for events that are highly associated with precautionary reports, the numerator (A) artificially increases to such an extent that it produces spurious signals for these events. In addition to the masking effect described above, precautionary reports could delay the identification of safety signals, by increasing the time-to-detection due to an increased background-reporting rate (B), which requires more reports with the event of interest (A) over time to create an SDR.

The majority of the spurious signals that are triggered by precautionary reports relate to *extraneous* events, for which the biological plausibility as to whether the event is caused by the medicinal product is questionable. Examples of such extraneous events that create spurious signals are "euthanasia" and "hospice care" (events that are not informative) or, for instance, events related to the indication (e.g., "hemoglobin increased" for erythropoietin) or the natural course of the underlying disease (e.g., "cancer pain" for bisphosphonate). The five most reported events for the three case products, for example, are all extraneous events (**Table 1**). There are also spurious signals that do not refer to extraneous events (e.g., "lung infection" for erythropoietin). Nonetheless, these events still lack a causal relationship with the suspected medicinal product and could be related to comorbidities.

There always remains a possibility that some of the events related to the indication or underlying disease could represent a paradoxical adverse event or point towards a lack of therapeutic effect.[20,21] However, as long as reporters of such an event do not provide any motive or rationale for a paradoxical adverse event or potential lack of effect, it hampers any meaningful interpretation of such safety signals. Therefore, their negative impact on signal detection that is demonstrated in this article; in our view, does not justify the potential (but limited) gains from these reports.

Table 1 Five most reported events for the precautionary reports of each of the three case products (in descending order)

Event (as MedDRA PT)	Medicinal product/events associations as a % of total for each case product	% of reports with the specific event classified as precautionary report
Erythropoietin		
Death	36%	99%
Hospitalization	15%	87%
Off label use	3%	78%
Dialysis	2%	90%
Terminal state	1%	68%
Bisphosphonate		
Death	9%	95%
Malignant neoplasm progression	5%	79%
Terminal state	5%	87%
General physical health deterioration	3%	81%
Neoplasm progression	3%	83%
Endothelin receptor antagonist		
Death	14%	84%
Right ventricular failure	2%	75%
Cardiac failure	1%	68%
Pulmonary arterial hypertension	1%	84%
Pulmonary hypertension	1%	62%

MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term.

Limited information exists in the literature to explain the rationale behind precautionary reports, but it has been pointed out that current pharmacovigilance legislations and guidelines could play an important role. The guideline on Good Pharmacovigilance Practice (GVP) Module VI states that reports obtained from organized data collection systems should be considered as solicited reports and are subject to appropriate causality assessments to assess whether they meet the criteria for reporting.[5] According to the ICH guideline for Good Clinical Practice (GCP), all events for which the causal relationship between the medicinal product and the event cannot be ruled out should be considered an ADR.[5,19]

Some documents found in the literature point out the challenges that MAHs encounter when trying to perform causality assessments and highlight the potential implications of these guidelines. These documents emphasize that reports from PSPs often lack the necessary information required for an appropriate causality assessment.[16,17] Moreover, efforts of MAHs to retrieve such important missing information during follow-up are extremely difficult or even impossible due to patient anonymity in these programs.[22,23] This inevitably prevents MAHs from being able perform an appropriate causality assessment, and thus to rule out any causal relationship. Hence, these reports meet the definition of an ADR report from a regulatory perspective and have to be submitted by MAHs as part of their regulatory obligation. That this also occurs in daily practice can be observed in company statements in the EU and US commenting on guideline proposals and a blog post commenting on the above-mentioned

Table 2 Overview of SDR detection before and after exclusion of precautionary reports from the ADR database

Case product	Medicinal product/event associations [*N*]	Medicinal product/event associations from reports classified as precautionary reports [*N* (%)]	Number of SDRs detected [*N*]		Change in SDR detection	
			Before exclusion of precautionary reports	After exclusion of precautionary reports	SDRs no longer appearing [*N* (%)]	Unmasked SDRs [*N* (%)]
Erythropoietin	4,327	3,591 (83%)	54	43	27 (50%)	16 (37%)
Bisphosphonate	6,531	4,922 (75%)	175	82	101 (58%)	8 (10%)
Endothelin receptor antagonist	1,555	716 (46%)	64	43	26 (41%)	5 (12%)

SDR, signal of disproportionate reporting.

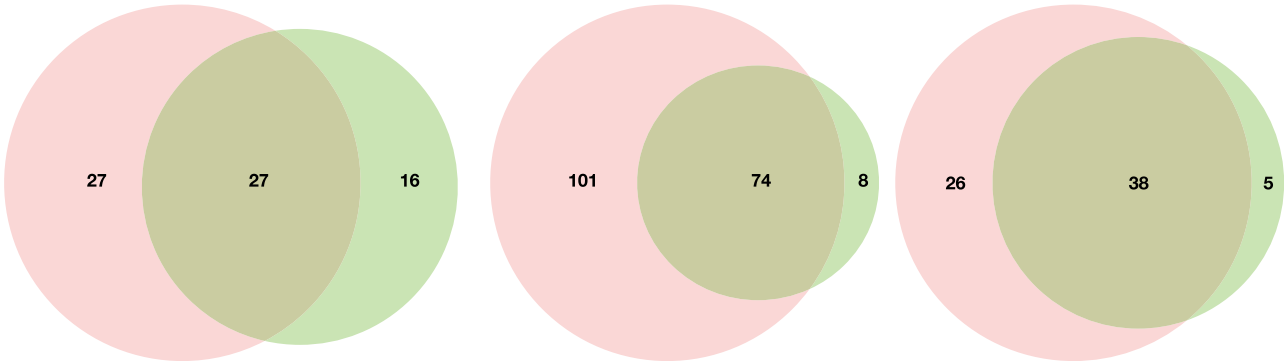

Figure 2 Venn diagram of the number of SDRs detected before and after exclusion of the precautionary reports from the ADR database for the three case products. From left to right: Erythropoietin, bisphosphonate, and endothelin receptor antagonist; red circle: SDRs detected before exclusion of precautionary reports; green circle: SDRs detected after exclusion of precautionary reports; overlap: SDRs detected before and after exclusion of precautionary reports. [Color figure can be viewed at cpt-journal.com]

ISMP report, stating that MAHs acknowledge a positive causal relationship if the required information for such an assessment is not available.[23–25]

Despite the fact that reports derived from organized data collection systems should generally be considered as solicited reports, the actual majority of the (precautionary) reports from organized data collection systems that we have identified in this study relate to spontaneous reports (**Figure 1**). For spontaneous reports, different guidelines are in place. In this case, the ICH E2D guideline states that if an event is spontaneously reported, even if the relationship is unknown or unstated, it implies causality and meets the definition of an ADR.[26] This was substantiated by company statements found in the case narratives of such reports, stating that it is company policy to consider every spontaneous report as *suspected,* including reports for which the causality was unsuspected.

Regardless of the report type, we believe that three additional factors contribute to the precautionary reporting bias: 1) the large volume of reports that MAHs generally receive from PSPs due to extensive patient contact; 2) the 15-day time frame in which MAHs are required to submit serious events that they have been informed of to regulatory authorities; and 3) possible legal consequences and severe penalties that MAHs face if events are not submitted (in time).[27–30]

There are a number of limitations that apply to this study. The text-mining algorithm was prone to spelling/typing errors and changes in the textual structure and wording of case narratives, which could have resulted in an underestimation of the actual number of precautionary reports identified. Another limitation of this study is the selection of the three case products based on the MedDRA PT "death." Due to this inclusion criterion, medicinal products were selected that were more likely related to severe diseases with high mortalities. Furthermore, this study was only performed in a single national ADR database, which means that the results should be extrapolated with caution. Nonetheless, since this study primarily served the purpose to demonstrate the existence of the precautionary reporting bias, this approach was regarded as sufficiently appropriate.

We believe that the results of this study have EU-wide implications. Since the pharmacovigilance guidelines are effective at the EU level and organized data collection systems are widely integrated in EU healthcare systems, we expect the precautionary reporting bias to be also affecting other national ADR databases and aggregated ADR databases, such as EudraVigilance or the WHO pharmacovigilance database "VigiBase." We recommend replicating this study in other ADR databases. A more robust algorithm or a case-by-case assessment could improve the identification of precautionary reports. Machine-learning techniques could help to develop and improve text-mining algorithms that can adapt to new case narrative structures (and changes over time). This not only allows for screening more complex narratives, but also for data stratification based on causality, which could improve statistical signal detection methods. Furthermore, we believe that a revision of the E2B-data elements could help identify reports from organized data collection systems, allowing for more stratified analysis. We also recommend an analysis of the potential increase of time-to-detection (of safety signals) caused by precautionary reports.

The precautionary reporting bias is an example of the limited alignment between regulation and (clinical) practice. In general, regulators and MAHs act in a rational manner: regulators set low thresholds as to what needs to be considered an ADR to minimize the chance that actual ADRs are not being reported and MAHs aim to be compliant with current regulations. However, as this study demonstrates, this rational behavior is at the expense of safety signal detection and, consequently, has implications for the protection of public health. To solve this issue, we propose: 1) a more robust definition and clear understanding of a reportable event, and 2) better alignment between regulators and MAHs as to which reports need to be submitted to regulatory authorities. This study also tries to contribute to the discussion from a scientific perspective. In our opinion, the regulatory science community has an important role in supporting the continuous dialog between stakeholders and evaluating current practices to learn how we can optimally use the pharmacovigilance system.

In conclusion, the results of this study demonstrate for the first time the existence of the precautionary reporting bias and its suppressing effect on statistical signal detection methods in ADR databases. The accumulation of nonvalue-added precautionary

Table 3 An overview of the unmasked signals of disproportionate reporting (SDRs) after exclusion of precautionary reports from the ADR database

Case product	Unmasked SDR (PT)
Erythropoietin	Deep vein thrombosis[a,b]
	Drug ineffective[a]
	Feeling abnormal[a]
	Fluid retention[b]
	Infection[a]
	Influenza[a]
	Influenza like illness[a]
	Injection site pain[a,b]
	Limb discomfort[a]
	Malaise
	Myocardial infarction
	Pain[a]
	Pallor
	Pyrexia[a]
	Renal failure
	Renal impairment
Bisphosphonate	Arthralgia[b]
	Arthritis[a,b]
	Blood glucose increased[a]
	Candida infection[a]
	Eye pain[a,b]
	Hypotension[a,b]
	Swelling[a,b]
	Tooth disorder[a,b]
Endothelin receptor antagonist	Abortion spontaneous[a]
	Anaemia[a,b]
	Deep vein thrombosis[a]
	Myocardial infarction
	Weight increased[a]

[a]SDRs that represent events considered potential safety issues according to our definition, as they are not related to the underlying disease, the indication, the (mis-) use or a patient outcome. [b]SDRs that represent events that are listed in the Summary of Product Characteristic (SmPC) section on adverse reactions.

reports in ADR databases impede the optimal use of the pharmacovigilance system and thus the protection of public health. The exclusion of precautionary reports from the ADR database resulted in the unmasking of previously undetected safety signals. We therefore urge stakeholders to address this issue and improve the alignment between regulation and practice in this area. This will not only decrease burdens for regulators and MAHs but also increase the effectiveness and efficiency of pharmacovigilance systems and thus contribute to a better public health protection.

Box 1 Calculation of the reporting odds ratio (ROR) based on the two-by-two contingency table

Two-by-two contingency table:

	Event of interest	All other events
Medicinal product of interest	a	b
All other medicinal products	c	d

The ROR is computed as: $\frac{(a/b)}{(c/d)}$

The standard error (se) of the natural logarithm of the ROR is as follows:

$$SE = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

The lower bound of the 95% confidence interval (CI) for the ROR is then calculated as:

$$95\%CI \text{ (lower bound)} = e^{\ln(ROR) - 1.96 * se}$$

METHODS

The Netherlands has a long tradition of PSPs and other forms of organized data collections systems that are integrated in the national healthcare system. The Dutch ADR database is therefore a viable setting to conduct this study since the database is complemented with serious spontaneous and solicited reports received via the MAH.

All ADR reports that were reported since the start of data collection were included in the analysis. Events were coded according to the MedDRA PT. Medicinal products were coded according to the Anatomical Therapeutic Chemical (ATC) classification system. PL/SQL Developer Version 11.0.6.1776 was used for the extraction of ADR data from the database. Statistical analyses were performed using R statistical software v. 3.2.2.

We approached this assessment with three case studies: 1) an erythropoietin for the treatment of anemia in patients with chronic renal failure and chemotherapy; 2) a bisphosphonate for the treatment of osteoporosis and bone diseases in patients with cancers; and 3) an endothelin receptor antagonist for the treatment of pulmonary artery hypertension (PAH). We selected our case products based on the largest number of ADR reports from MAHs with the MedDRA PT "death" in the ADR database, as this could potentially indicate the existence of precautionary reports.[16,18] We selected three case products from three different MAHs, which have different indications and an assessable case narrative structure.

Case narratives of all reports were screened with a text-mining algorithm we developed for this study to determine if a report should be allocated to the "precautionary report" category or whether it is a "confirmed ADR report." Reports were classified as precautionary reports if the information in the case narrative stated that the causal relationship between the medicinal product and the event was unknown, unsuspected, not related, not assessed, or not provided (e.g., due to insufficient information to establish a causal relationship). See **Box 2** for an example of a case narrative of a spontaneous report that was classified as a precautionary report. In contrast, if the case narrative stated that the causal relationship between the suspected medicinal product and the event (or to one of the events) was *likely, probable, possible, or unlikely (as there is still a possibility),* ADR reports were classified as a confirmed ADR report. In line with our conservative approach, we classified reports that were not allocated to either category as a confirmed ADR report. This assessment was done at the level of

Box 2 Example of a spontaneous report for the bisphosphonate that was classified as precautionary report

This is an initial spontaneous report from a nurse for a patient support program received on <*date*> combined with follow-up from a patient's daughter received on <*date*>. This report refers to a 73-year-old male patient who received the *bisphosphonate* for the treatment of metastasized prostate carcinoma from an unspecified date. The last administration of the *bisphosphonate* occurred on <*date*>. At that time the patient's condition was deteriorating. Seriousness, causality assessment, and event outcome were not provided. The patient died <*21 days after the last administration*>. The cause of death and a causality assessment were not provided.

Confidential information has been removed/adjusted (italic).

the report: if a report was classified as both a precautionary report and a confirmed ADR report, it was ultimately allocated to the confirmed ADR report category. Two scenarios may result in duplicate classification: 1) a report with two (or more) events, of which for one event a suspected causal relationship with the medicinal product exists, whereas this is not the case for the other event(s), or 2) a report with an event for which the causal relationship was initially not established (e.g., due to insufficient information), but was later confirmed during follow-up. The text-mining algorithm was refined until saturation, i.e., further adjustments did not lead to any substantial improvements in the identification of precautionary reports. Both report categories were further stratified by report type, to differentiate between spontaneous and solicited reports, and report source, to identify reports received from an organized data collections system. Two assessors (K.K., J.S.) reviewed the allocated report categories in the process of developing the text-mining algorithm by reexamining case narratives with a random sampling.

For each of the three cases, SDR detection was performed before and after we excluded the precautionary reports from the ADR database. The ROR was used as the measure of disproportionality for the detection of SDRs, as this is the standard method applied by the Netherlands Pharmacovigilance Centre Lareb and the EMA, with a threshold for the lower bound of the 95% confidence interval (CI) of one and a minimum of three reported cases of medicinal product/event associations corresponding to the general standards of the EMA.[9] SDR detection analysis was performed at the level of medicinal product/event associations.

Three clinical experts from the Netherlands Pharmacovigilance Centre Lareb independently performed an assessment of all SDRs detected before and after exclusion of precautionary reports from the database, to identify SDRs that relate to events associated with the indication, the natural course of the underlying disease, other treatments for the disease, the (mis-) use of the medicinal product (e.g., "off-label use"), or events referring to patient outcomes (e.g., "terminal state"). The possibility that an SDR relating to such an event represents an actual ADR of the medicinal product can generally be eliminated, as the obvious cause is disease-related and not product-related. Inversely, this approach allowed us to consider every SDR that does not relate to any of the above-mentioned event categories, as a safety signal requiring further evaluation due to the absence of obvious confounders. For all newly detected SDRs after exclusion of the precautionary reports from the ADR database (referred to as *unmasked* SDRs), the percentage of SDRs requiring further evaluation was calculated. The assessment was done in a blinded fashion; i.e., clinical experts did not know which SDRs were detected before and/or after the exclusion of the precautionary reports from the ADR database. Moreover, for each unmasked SDR, we assessed whether the event is mentioned in the SmPC undesirable effects section 4.8.

ACKNOWLEDGMENTS

We thank the two additional clinical experts from the Netherlands Pharmacovigilance Centre Lareb, Annet van Boekel and Annemarie Muller-Hansma, for their time in assessing and evaluating signals of disproportionate reporting that have been detected and investigated as part of this study.

CONFLICT OF INTEREST

All authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTIONS

K.K., M.B., and P.S. conceived the idea for this study. K.K. and J.S. contributed equally to this work. K.K., J.S., M.B., E.P., H.L., and P.S. wrote the article; K.K., J.S., M.B., E.P., and P.S. designed the research; K.K. and J.S. performed the research; K.K. and J.S. analyzed the data.

© 2017 American Society for Clinical Pharmacology and Therapeutics

1. Wise, L., Parkinson, J., Raine, J. & Breckenridge, A. New approaches to drug safety: a pharmacovigilance tool kit. *Nat. Rev. Drug Discov.* **8**, 779–782 (2009).
2. European Commission. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf> (accessed 31 Aug. 2017).
3. European Commission. Regulation (EC) No 726/2004 of The European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:pdf> (accessed 31 Aug. 2017).
4. European Medicines Agency. EU Individual Case Safety Report (ICSR) Implementation Guide. <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/04/WC500165979.pdf> (accessed 27 Feb. 2017).
5. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VI — Management and reporting of adverse reactions to medicinal products. <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500123203.pdf> (accessed 27 Feb. 2017).
6. Puijenbroek, E. & Grootheest, K. Organization of Pharmacovigilance in the Netherlands. In Mann's Pharmacovigilance (eds. Andrews, E.B., Moore, N.) 213–216 (Oxford, UK, John Wiley & Sons; 2014).
7. Hauben, M. & Aronson, J.K. Defining 'signal' and its subtypes in pharmacovigilance based on a systematic review of previous definitions. *Drug Saf.* **32**, 99–110 (2009).
8. Scholl, J.H.G. & van Puijenbroek, E.P. The value of time-to-onset in statistical signal detection of adverse drug reactions: a comparison with disproportionality analysis in spontaneous reports from the Netherlands: Time-to-onset in signal detection of ADRs. *Pharmacoepidemiol. Drug Saf.* **25**, 1361–1367 (2016).
9. European Medicines Agency. Screening for adverse reactions in EudraVigilance. <http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218606.pdf> (accessed 27 Feb. 2017).
10. Pariente, A. *et al*. A potential competition bias in the detection of safety signals from spontaneous reporting databases. *Pharmacoepidemiol. Drug Saf.* **19**, 1166–1171 (2010).
11. Arnaud, M. *et al*. A method for the minimization of competition bias in signal detection from spontaneous reporting databases. *Drug Saf.* **39**, 251–260 (2016).

12. Gould, A.L. Practical pharmacovigilance analysis strategies. *Pharmacoepidemiol. Drug Saf.* **12**, 559–574 (2003).
13. Almenoff, J. *et al*. Perspectives on the use of data mining in pharmacovigilance. *Drug Saf.* **28**, 981–1007 (2005).
14. Hauben, M. & Hochberg, A. The importance of reporting negative findings in data mining: the example of exenatide and pancreatitis. *Pharm. Med.* **22**, 215–219 (2008).
15. Salvo, F. *et al*. A potential event-competition bias in safety signal detection: results from a spontaneous reporting research database in France. *Drug Saf.* **36**, 565–572 (2013).
16. Sookoo, A. An inspector's perspective — considerations for patient support and reimbursement programmes (Stakeholder Meeting, 7th June 2013). <http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/06/WC500144661.pdf> (accessed 27 Feb. 2017).
17. Council for International Organizations of Medical Sciences. Current Challenges in Pharmacovigilance: Pragmatic Approaches (Report of CIOMS Working Group V). <https://cioms.ch/wp-content/uploads/2017/01/Group5_Pharmacovigilance.pdf> (accessed 31 Aug. 2017).
18. Institute for Safe Medication Practices. A critique of A Key Drug Safety Reporting System. <http://www.ismp.org/QuarterWatch/pdf>s/2014Q1.pdf> (accessed 27 Feb. 2017).
19. International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH). Guideline for good clinical practice. <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf> (accessed 1 Mar. 2017).
20. Windsor, A.C. *et al*. Paradoxical clinical deterioration despite near-complete pathological response to neoadjuvant chemotherapy for locally advanced gastro-oesophageal adenocarcinoma. *Surg. Oncol.* **4**, 277–279 (1995).
21. Sfikakis, P.P., Iliopoulos, A., Elezoglou, A., Kittas, C. & Stratigos, A. Psoriasis induced by anti-tumor necrosis factor therapy: A paradoxical adverse reaction. *Arthritis Rheum.* **52**, 2513–2518 (2005).
22. Pharmaceutical Industry Associations. Management of Safety Data Originating from Patient Support and Market Research Programmes — Current Challenges from Pharmaceutical Industry and Proposals to Move Forward. <http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/06/WC500144670.pdf> (accessed 1 Mar. 2017).
23. Johnson & Johnson. Commentary on 'Safety requirements for human drug and biological products.' <https://www.fda.gov/ohrms/dockets/dailys/03/oct03/101703/00N-1484-emc-000052-02.doc> (accessed 1 Mar. 2017).
24. Balderson, D. Meeting Regulatory Agency Expectations on Reporting and Quality of ICSRs. <http://www.sciformix.com/safety-risk-management-blog/meeting-regulatory-agency-expectations-wrt-reporting-and-quality-of-icsrs/> (accessed 1 Mar. 2017).
25. European Federation of Pharmaceutical Industries and Associations. Submission of comments on legislative proposals to strengthen and rationalise the EU system of pharmacovigilance. <http://ec.europa.eu/health//sites/health/files/files/pharmacovigilance/docs/2007_02_26/48.pdf> (accessed 1 Mar. 2017).
26. International Council for Harmonisation of technical requirements for pharmaceuticals for human use (ICH). Post-approval safety data management: definitions and standards for expedited reporting. <https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf> (accessed 1 Mar. 2017).
27. European Medicines Agency. European Medicines Agency acts on deficiencies in Roche medicines-safety reporting. <http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/06/WC500129047.pdf> (accessed 1 Mar. 2017).
28. European Medicines Agency. European Medicines Agency starts infringement procedure to investigate Roche's alleged non-compliance with pharmacovigilance obligations. <http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/10/WC500134176.pdf> (accessed 1 Mar. 2017).
29. European Medicines Agency. Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period. <http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127657.pdf> (accessed 1 Mar. 2017).
30. Medicines Evaluation Board. ADR reporting requirements based on pharmacovigilance legislation. <https://english.cbg-meb.nl/human/for-marketing-authorisation-holders/contents/post-marketing-authorisation/reporting-adverse-events> (accessed 1 Mar. 2017).