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Published in:
Clinical Pharmacology and Therapeutics

DOI:
10.1002/cpt.1775

Publication date:
2020

Document Version
Publisher's PDF, also known as Version of record

Ability of Primary Care Health Databases to Assess Medicinal Products Discussed by the European Union Pharmacovigilance Risk Assessment Committee

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This study measured the exposure to different categories of medicinal products discussed by the European Union (EU) Pharmacovigilance Risk Assessment Committee from September to November 2018 in four electronic primary care health databases: IQVIA Medical Research Data-UK, IQVIA Medical Research Data-France, IQVIA Medical Research Data-Germany, and Clinical Practice Research Datalink Aurum, in the entire lifespan of each database until August 31, 2018. The assessment of 83 centrally authorized products and 45 nationally authorized products showed that coverage was better for products marketed for longer duration and worse for orphan drugs. The ability to detect associations against hypothetical comparators was better for more common events and for larger effect sizes. Coverage of advanced therapies was worse for those typically administered in a specialized rather than primary care setting. This study shows that to enable better informed regulatory decisions there is a need to access complementary data sources, particularly capturing secondary care prescribing.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Electronic primary care health databases are used by regulators to assess the need for and the impact of postlicensing regulatory interventions.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We measured the extent to which exposure to different categories of medication was covered in the electronic primary care health databases available to the European Medicines Agency.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ More advanced and more recently authorized medicinal products had less coverage in the available databases compared to more established, nationally licensed products.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ To optimize the regulatory decision-making process regulators need better access to data that allows the postlicensing assessment of newer, more advanced therapies. This study shows that many such therapies are not used in the primary care setting and regulators should seek to gain access to complementary data sources, particularly those capturing the use of medicines in specialist settings.

The European Union (EU)'s pharmacovigilance system has at its core the European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC) with the responsibility to protect patients by ensuring that the safety of medicines on the market are under continual review. This task includes the detection and assessment of the risk of adverse reactions, while taking the therapeutic effect of the medicine into account.[1,2] The EU pharmacovigilance system is, therefore, underpinned by scientific evaluation of all the evidence available, including valid data on the utilization and effects of medicines in clinical practice.

The EMA supports medicines evaluation by analyzing data for products or groups of products, particularly where it is hard to identify a single marketing authorization holder from three commercially available electronic primary care health databases (primary EHDs) that it accesses to assess drug utilization, risks of medicines, and effectiveness of risk minimization measures.[3–9] These primary

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Received October 17, 2019; accepted December 23, 2019. doi:10.1002/cpt.1775

EHDs include routinely collected patient data from a network or a sample of mainly general practitioners (GPs) practices. Primary EHDs represent an optimal data source for medicines evaluation by capturing detailed information on patients' health status, drugs prescribed, and medical outcomes. In addition, their large size may allow the study of rare events and their representativeness of routine clinical care may allow the study of real-world effects of medicines prescribed in the community. Due to their retrospective nature, they can also be analyzed rapidly.[10]

A previous study has reported that some drug exposures may be incompletely captured in primary EHDs because they are utilized only in secondary care (hospital) settings or in specialized institutions or because they are not reimbursed.[11] For the EMA, this limitation would be relevant in light of its responsibility for the authorization and monitoring of centrally authorized products (CAPs) in the European Union. The centralized procedure is compulsory for medicine used to treat specific conditions (for example, HIV/AIDS, diabetes, and neurodegenerative diseases), medicines derived from biotechnology processes, advanced-therapy medicines (for example, gene therapies), and orphan medicines (for rare diseases) and is optional for other medicines that are significant innovations or which are of public health interest. In practice, this means that the majority of new medicines pass through the centralized authorization procedure, which infers EU-wide marketing authorization. In 2018, 84 medicines were recommended for approval by the EMA and for 58 of them (69.0%) the product information recommended initiation and supervision of the treatment by a specialist.[12] This feature may increase over time given the high number of marketing authorization applications for advanced therapy medicinal products (ATMPs—a class of products that include gene therapies, tissue engineered products, and somatic cell therapies) expected in the next few years. During January 2009 to June 2018, the EMA received a total of 564 requests relating to ATMPs: 286 requests for ATMP classification and 278 for scientific advice for these products.[13] Detailed information on prescriptions from secondary care in primary care databases, therefore, requires that patients from secondary care are routinely followed up in primary care, like in the United Kingdom, and that prescribing information from secondary care is shared with primary care and recorded in the patients' electronic records.

Empirical observations during PRAC meetings have shown that several products discussed by PRAC have limited or no exposure readily available in the primary EHDs available to the EMA and that complementary data sources would be needed for their assessment, such as claims data or patient registries.[14] If true, these observations would need to be considered by the EU pharmacovigilance system as regard to the type, characteristics, and complementary nature of data sources to be used to support the evaluations, and the data checks to be applied when planning studies. This issue also concerns marketing authorization holders, which may be required to provide additional data in the course of PRAC assessments.[2]

This evaluation was undertaken to systematically measure the exposure to prescribing for medicinal products included in topics discussed by the PRAC in primary EHDs and to identify characteristics associated with the exposure prevalence, such as type of authorization (at European level for CAPs or at the national level for nationally authorized products (NAPs)), duration of authorization, and therapeutic class. Four available primary EHDs were used for the study: IQVIA Medical Research Data-France (IMRD-France, formerly IMS-France), IQVIA Medical Research Data-Germany (IMRD-Germany, formerly IMS-Germany), IQVIA Medical Research Data-United Kingdom (IMRD-UK, incorporating data from THIN, a Cegedim Database), and the Clinical Practice Research Datalink (CPRD).

METHODS

Drug substances

We extracted from the time schedule of the PRAC plenary meetings of September, October, and November 2018, all substances or classes of substances included in regulatory procedures, except those related to risk management plans concerning products in the preauthorization phase (where no real-world data would be available prior to marketing), inspections, and organizational matters, which are not specific to authorized products.[15] This period was chosen to allow availability of contemporaneous data to the PRAC meetings. Taking 3 months in a row decreased the likelihood of duplication of substances given the time needed to collect and analyze additional information in the case of follow-up actions.

Primary electronic healthcare databases

As a first step in the analysis, we assessed the prescription counts for each country involved in the analysis: For England (digital.nhs.uk), for France (ameli.fr), and for Germany (wido.de). This information served as a background for consistency checks and was useful to clarify why some drugs were not represented in our databases. We then searched for drug exposure to each substance or class of substances in four electronic primary EHDs: IQVIA Medical Research Data-France (IMRD-France), IQVIA Medical Research Data-Germany (IMRD-Germany), IQVIA Medical Research Data-United Kingdom incorporating data from THIN, a Cegedim Database (IMRD-UK), and the Clinical Practice Research Datalink (CPRD) Aurum database. The three IMRD databases are contractually available to the EMA in-house.

IMRD-France collects anonymized electronic health records through a panel of GPs representing about 2% of physicians, weighted by age and sex of the physician, doctor region, and an indicator of the GP's volume of activity in terms of visits and consultations. In France, patients can visit a physician of choice whenever a medical need emerges, although they must visit a GP before going to a specialist in order to get reimbursement, except for pediatricians, gynecologists, and ophthalmologists. The coding system for medicinal products is based on the European Pharmaceutical Market Research Association (EphMRA). A drug dictionary with unique identifiers for each drug is provided with the database.

IMRD-Germany collects anonymized electron health records (EHRs) through a representative panel of GPs, some specialists in internal medicine, and other specialist physicians (~ 3% of all GPs in Germany), stratified for specialist group, region, community size, and age of physician. In Germany, patients can visit a physician of choice, including a specialist physician, whenever a medical need emerges. Parents often choose to consult a pediatrician directly for the health care of their child. The coding system and search method for medicinal products are similar to IMRD-France, but the drug dictionary is more detailed allowing for identification of originator/generic products and parallel imported products.

In the United Kingdom, GPs play a gatekeeper role in the healthcare system, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

IMRD-UK contains longitudinal electronic patient records extracted from the VISION practice management software, which has been contributed to by > 790 general practices across the United Kingdom covering ~ 6% of the UK population. Data are largely representative of the UK population in terms of age, sex, deprivation status, and geographic distribution. It contains GP prescriptions with medicinal products identified through a bespoke system of drug codes linked to generic drug names (substance names) or a substitute thereof in a drug and device dictionary. This dictionary is provided with the database.

Clinical Practice Research Datalink (CPRD) comprises anonymized computerized medical records of GPs from a UK-wide network of over 1,100 primary care practices covering about 15% of the population in August 2019. The CPRD comprises two complementary databases—CPRD GOLD (data collected from practices using VISION practice management software) and CPRD Aurum (data collected from practices using EMIS practice management software). As practices in CPRD GOLD and IMRD-UK overlap, analyses were restricted to CPRD Aurum practices. To further minimize the possibility of overlap between IMRD-UK data and CPRD Aurum, CPRD Aurum practices known to have switched from using Vision Practice Management software were also excluded. A total of 721 EMIS practices comprising of over 18 million patients were eligible for inclusion in the analysis. Drugs in the CPRD Aurum database are coded using the National Health System (NHS) dictionary of medicines and devices codes, and EMIS system-specific codes. Therapy code lists and medical codes, where applicable, were developed for this study using searches based on the drug substance, product name, and term in the CPRD Aurum product dictionary, and using Read codes and Read terms in the medical dictionary.

Data extraction

The following information was extracted from the PRAC time schedule: Month of PRAC meeting, regulatory procedure where the substance was included, substance name or class of substances, authorization type (CAP or NAP) of each substance, and product name for CAPs. If both authorization types existed for the same substance, the substance was classified as CAP. In cases where a drug class contained both CAPs and NAPs, the classification was based on the authorization type of the majority of substances. Drug classes "Fluoroquinolones," "Selective serotonin reuptake inhibitors," and "Hormonal contraceptives" were classified as NAPs and the class "Serotonin and noradrenaline reuptake inhibitors" was classified as CAP. For CAPs, information on authorization date in the European Union and orphan designation status (substance indicated for a condition with prevalence not higher than 5/10,000 in the European Union) was extracted from the EMA website; for NAPs, information on authorization status in the United Kingdom, France, and Germany and the date of first authorization in the European Union was extracted from public and nonpublic data from the EMA's Article 57 database.[16] In order to verify the marketing status of each substance, publicly available prescription or sales data in primary care were consulted for each country.[17–19] The therapeutic class for each substance was assigned based on the Anatomic Therapeutic Chemical (ATC) classification.[20]

Estimation of drug exposure

For each substance (or class of substances), the number of prescriptions and the number of patients receiving at least one prescription was searched during the entire lifespan of each database until August 31, 2018. For substances existing both alone and in combination, the search was made either for the individual component or for the combination, in line with the information provided in the PRAC time schedule. There was no restriction with regard to duration of follow-up, number of prescriptions, duration of prescriptions, or gaps between prescriptions. Prescriptions with missing dates were excluded. More than one prescription for the same substance on the same day counted as a single prescription. The end of observation for each patient was defined as the earliest of the patient transfer out date, the practice last collection date and the of August 31, 2018 (end of the evaluation period). All patients were required to have at least one day of follow-up on or before August 31, 2018.

Data analysis

Descriptive analyses include the number of substances without any prescription per database, authorization type and duration of authorization in three categories (< 2 years, 2–5 years, and > 5 years), and the median (with range) number of prescriptions and patients available per database, authorization type, and duration of authorization. The same statistics were calculated for the pooled data from each database.

To estimate the number of substances for which each database could meaningfully assess adverse events, we calculated the numbers of patient exposures required to detect a statistically significant adverse event associated with a range of theoretical relative risks (RRs) for CAPs and NAPs in different frequency categories. This was based on a hypothetical comparison of two proportions using a two-sided Fisher exact test with $\alpha = 0.05$, power = 0.90 and equal numbers of patients exposed to the drug of interest and a comparator. Effect sizes of a doubling and a four-times increase in events rate against a hypothetical comparator were used. Adverse event rates were based on the Summary of Product Characteristics adverse drug reaction frequencies and were conservatively taken from the least common end of the frequency ranges: 1 of 10 for "very common," 1 of 100 for "common," 1 of 1000 for "uncommon," 1 of 10,000 for "rare," and 1 of 100,000 for "very rare."

RESULTS

A total of 128 drug substances or substance classes were extracted from the topics listed in the time schedules of the PRAC meetings for September, October, and November 2018, including 83 CAPs (64.8%) and 45 NAPs (35.2%); 51 substances (39.8%) were discussed in the context of assessments of periodic safety update reports and 31 substances (24.2%) in the context of assessments of safety signals (**Table 1**). The most frequently discussed substances were antineoplastic agents or immunomodulators for CAPs (36.1%) and those indicated for the nervous system for NAPs (28.9%). The list of substances with their characteristics is provided in the **Supplementary Table**. Among the NAPs, four substances discussed by PRAC were

Table 1 Number of substances extracted from PRAC time schedules for September, October, and November 2018 by regulatory procedure[15] and authorization type

Regulatory procedure	CAPs	NAPs	Total
PASS protocol or results	7	3	10
PSUR	28	23	51
Referral	2	0	2
Renewal or reassessment	4	0	4
Request for advice	4	10	14
RMP postauthorization	10	0	10
Safety signal	28	9	37
Total	83	45	128

CAPs, centrally authorized products; NAPs, nationally authorized products; PASS, postauthorization safety study; PSUR, periodic safety update report; RMP, risk management plan.

not authorized in the United Kingdom, France, or Germany, two were authorized in France only, and one each were authorized only in the United Kingdom and Germany. Among CAPs, 6 (7.2%) had been authorized for < 2 years on September 1, 2018, 20 (24.1%) had been authorized for 2–5 years, and 57 (68.7%) had been authorized for > 5 years (**Table 2**). Where marketed, all NAPs had been nationally authorized for > 5 years.

There was some variability among the four databases in the percentages of substances with at least one prescription in primary care (**Table 2**). For all CAPs, it was 59.0% in IMRD-France, 89.2% in IMRD-Germany, 78.3% in IMRD-UK, and 86.7% in CPRD Aurum; in all cases, the proportion increased with increasing duration of authorization. For NAPs, the percentages were 73.3%, 86.7%, 75.6%, and 77.8%, respectively. The higher percentages in Germany are not explained by the inclusion in the German database of patients consulting primary care specialists as opposed to GPs as only one substance not prescribed by GPs was prescribed by specialists and that was used in four patients only. Broadly, there

Table 2 Number and percentage of CAP and NAP substances (or classes of substances) with at least one prescription, median (IQR) number of prescriptions, and median (IQR) number of patients per authorization type and duration of authoriation for CAPs[a]

	CAPs				
	Duration of authorization (years)				
	< 2	2–5	> 5	All	NAPs
All substances, *n*	6	20	57	83	45
IMRD-France					
n (%) substances with ≥ 1 prescription	1 (16.7)	10 (50.0)	38 (66.7)	49 (59.0)	33 (73.3)
Median (IQR) of prescriptions	0 (0–0)	1 (0–77)	74 (0–7,413)	15 (0–5,069)	6,709 (0–127,953)
Median (IQR) of patients	0 (0–0)	1 (0–40)	32 (0–2,320)	14 (0–1,477)	4,074 (0–32,701)
IMRD-Germany					
n (%) substances with ≥ 1 prescription	4 (66.7)	17 (85.0)	53 (93.0)	74 (89.2)	39 (86.7)
Median (IQR) of prescriptions	174 (0–709)	536 (69–5,307)	16,127 (1,354–127,467)	6,204 (343–69,411)	103,577 (181–585,347)
Median (IQR) of patients	34.5 (0–140)	168.5 (15–1,458)	2,339 (239–31,533)	1,219 (60–18,934)	15,973 (84–208,522)
IMRD-UK					
n (%) substance with ≥ 1 prescription	3 (50.0)	15 (75.0)	47 (82.5)	65 (78.3)	34 (75.6)
Median (IQR)—prescriptions	0.5 (0–2)	22 (1–941)	846 (16–246,318)	100 (1–65,081)	129,419 (7–2,059,555)
Median (IQR)—patients	0.5 (0–2)	15.5 (1–179)	245.0 (7–9,906)	67 (1–4,363)	8,528 (7–202,276)
CPRD Aurum					
n (%) substances with > 1 prescription	3 (50.0)	19 (95.0)	50 (87.7)	72 (86.7)	35 (77.8)
Median (IQR) of prescriptions	1 (0–10)	126.5 (18–1,627)	1,611 (43–200,183)	460 (12–83,560)	179,339 (15–2,405,014)
Median (IQR) of patients	0.5 (0–9)	121.5 (17–483)	499 (33–11,315)	345 (11–7,265)	10,690 (10–250,170)
Pooled data					
n (%) substances with > 1 prescription	4 (66.7)	20 (100)	54 (94.7)	78 (94.0)	42 (93.3)
Median (IQR) of prescriptions	179.5 (0–713)	1,038.5 (97–15,526)	36,112 (3,629–749,636)	9,133 (402–237,749)	582,925 (13,583–5,357,804)
Median (IQR) of patients	39.5 (0–143)	573 (35–2,460)	5,616 (420–70,195)	1,657 (93–38,867)	249,422 (3,010–780,308)

CAPs, centrally authorized products; CPRD, Clinical Practice Research Datalink; IMRD, IQVIA Medical Research Data; IQR, interquartile range; NAPs, nationally authorized products.
[a]All NAPs were authorized for > 5 years.

was consistency between the two UK data sources, which shared 11 CAPs and 10 NAPs that had no patient exposure in both data sources.

The number of CAP substances with at least one prescription, the median number of patients with a prescription, and the median number of prescriptions increased by duration of authorization, although the numbers are low for CAPs with < 2 years of authorization (**Table 2**). A characterization of substances with no prescribing is shown in **Table 3** for each database. Factors associated with nonprescribed drugs varied by country, for example, with reimbursement being a determining factor in France and the number of many "hospital only" drugs in the UK databases. Overall, the IMRD-Germany data had the lowest level of nonuse.

Ten CAPs were orphan medicinal products of which five were antineoplastic agents. Across all databases, just 2 of 10 orphan medicinal products had no patients exposed; however, the pooled number of patients exposed for each database was low, with a maximum of 143 patients being exposed across all data sources and 6 of the 10 orphan medicinal products having < 10 patients exposed.

Tables 4 and 5 show the ability of the databases to detect significantly different event rates for effects of various sizes in a hypothetical comparison with an equal number of comparator patients.

None of the individual databases would be able to detect a doubling in effect size for the majority of CAPs (**Table 4**) for "common," "uncommon," "rare,"or "very rare" events, or NAPs (**Table 5**) for "uncommon," "rare," or "very rare" events. Where the effect size was greater, with a four times increased risk, the ability to detect a statistically significant difference was also greater, but still only covered a minority of CAPs for "uncommon," "rare," and "very rare" events, and "rare" and "very rare" events for NAPs.

An analysis of the pooled data, where the numbers of patients exposed from each data source were combined, would allow the detection of an "uncommon" adverse event associated with a doubling of risk in 26.5% of CAPs and 60.0% of NAPs. For events that were "rare" or "very rare," the proportion of CAPs would be much lower (4.8% and 0%, respectively, for the CAPs; 40.0% and 11.1% for NAPs). For a larger effect size, where the hypothetical increase in events rate was fourfold, the ability to detect statistically significant differences was greater for "uncommon" events (38.6% of CAPs, and 71.1% of NAPs). However, this remained low for "rare" and "very rare" events with only a minority of associations being meaningfully tested (19.3% and 3.6%, respectively, for CAPs, and 57.8% and 28.9% for NAPs).

Table 3 Characterization of CAP and NAP substances with zero patient counts

IMRD-France
34 CAPs
16 not actively marketed
6 oncologic (most likely hospital only)
12 restricted use (e.g., only reimbursed for in-hospital use)
12 NAPs
5 unlicensed or not actively marketed
7 not reimbursed or restricted use (e.g., only reimbursed for in-hospital use)
IMRD-Germany
9 CAPs
3 not actively marketed
3 oncologic (most likely hospital only)
2 for rare/orphaned conditions (likely only to be used in a specialized setting)
1 hospital only drug
6 NAPs
3 unlicensed or not actively marketed
3 likely to be used in hospital or specialized settings only
IMRD-UK
18 CAPs
4 not actively marketed
7 oncologic
4 for rare/orphaned conditions
3 unlikely to be used in the primary care
11 NAPs
5 unlicensed or not actively marketed
6 unlikely to be used in the primary care
CPRD Aurum
11 CAPs
4 not actively marketed
3 oncologic (most likely hospital only)
1 for rare/orphaned conditions
3 unlikely to be used in the primary care
10 NAPs
5 unlicensed or not actively marketed
5 unlikely to be used in the primary care

CAPs, centrally authorized products; CPRD, Clinical Practice Research Datalink; IMRD, IQVIA Medical Research Data; NAPs, nationally authorized products.

DISCUSSION

Multiple potential sources of data may be used in the regulatory decision making, including EHRs generated in both the primary and secondary care environments, administrative claims records, prescription event monitoring systems, prescription databases, and registries. Clinical information from these other sources may be used to complement data already available and to more effectively monitor the safety and efficacy of authorized medicines once marketed.[2] However, each of these data sources has strengths and limitations associated with its use and a clear understanding of these is essential to define where and when each data source can add the most value.

A recent descriptive analysis of the utility of EHDs for regulatory purposes found that 34 EHDs were relevant based on data availability for both drug exposure and outcomes, but this did not consider actual availability or prevalence of medicinal products.[21] Similarly, guidelines aiming to assist in the selection and use of data resources in pharmacoepidemiology recommend obtaining a thorough knowledge of the unique characteristics of each data source,

Table 4 Number and percentages of CAP substances discussed by PRAC (*n* = 83) for which a causal association with a suspected ADR could be investigated according to different background rates and strengths of association

Background risk	Association with RR of 2.0		Association of RR of 4.0	
(per number of patients)	Required[a] number of patients exposed	No (%:95% confidence interval) of substances that can be investigated	Required[a] number of patients exposed	No (%:95% confidence interval) of substances that can be investigated
Very common ≥(1/10)	282	FR: 25 (30.1: 21.3–40.7) DE: 51 (61.4: 50.7–71.2) UKTh: 33 (39.8: 29.9–50.5) UKCP: 42 (50.6: 40.1–61.1) All: 56 (67.5: 56.8–76.6)	47	FR: 32 (38.6: 28.8–49.3) DE: 65 (78.3: 68.3–85.8) UKTh: 45 (54.2: 43.6–64.5) UKCP: 56 (67.5: 56.8–76.6) All: 68 (81.9: 72.3–88.7)
Common (1/100)	3,220	FR: 15 (18.1: 11.3–27.7) DE: 30 (36.1: 26.6–46.9) UKTh: 25 (30.1: 21.3–40.7) UKCP: 28 (33.7: 24.5–44.4) All: 37 (44.6: 34.4–55.3)	585	FR: 23 (27.7: 19.2–38.2) DE: 47 (56.6: 45.9–66.8) UKTh: 30 (36.1: 26.6–46.9) UKCP: 33 (39.8: 29.9–50.5) All: 52 (62.7: 51.9–72.3)
Uncommon (1/1,000)	32,601	FR: 2 (2.4: 0.7–8.4) DE: 14 (16.9: 10.3–26.3) UKTh: 12 (14.5: 8.5–23.6) UKCP: 14 (16.9: 10.3–26.3) All: 22 (26.5: 18.2–36.9)	5,960	FR: 12 (14.5: 8.5–23.6) DE: 29 (34.9: 25.6–45.7) UKTh: 19 (22.9: 15.2–33.0) UKCP: 24 (28.9: 20.3–39.4) All: 32 (38.6: 28.8–49.3)
Rare (1/10,000)	326,417	FR: 0 (0.0: 0.0–4.4) DE: 0 (0.0: 0.0–4.4) UKTh: 1 (1.2: 0.2–6.5) UKCP: 1 (1.2: 0.2–6.5) All: 4 (4.8: 1.9–11.7)	59,708	FR: 2 (2.4: 0.7–8.4) DE: 10 (12.0: 6.7–20.8) UKTh: 8 (9.6: 5.0–17.9) UKCP: 9 (10.8: 5.8–19.3) All: 16 (19.3: 12.2–29.0)
Very rare (1/100,000)	3,264,571	FR: 0 (0.0: 0.0–4.4) DE: 0 (0.0: 0.0–4.4) UKTh: 0 (0.0: 0.0–4.4) UKCP: 0 (0.0: 0.0–4.4) All: 0 (0.0: 0.0–4.4)	597,186	FR: 0 (0.0: 0.0–4.4) DE: 0 (0.0: 0.0–4.4) UKTh: 1 (1.2: 0.2–6.5) UKCP: 1 (1.2: 0.2–6.5) All: 3 (3.6: 1.2–10.1)

ADR, adverse drug reaction; All, pooled data; CAP, centrally authorized products; DE, Germany; FR, France; IMRD, IQVIA Medical Research Data; PRAC, Pharmacovigilance Risk Assessment Committee; RR, relative risk; UKCP, Clinical Practice Research Datalink; UKTh, IMRD-United Kingdom.
[a]Based on a hypothetical comparison of two proportions using a two-sided Fisher exact test with $\alpha = 0.05$, power = 0.90, and equal numbers of patients exposed in the drug of interest and comparator cohorts.

but not to go beyond general recommendations in terms of evaluation of exposure to medicinal products.[10,22,23]

Our analysis has shown large differences among the four databases in the availability of CAPs and NAPs (as identified from substances with at least one prescription) and the number of patients representing the population for a potential drug utilization or outcome study. The German data covered a wider array of medicinal products than the other data sources. This probably reflects the fact that in Germany there are fewer restrictions on what can be prescribed by GPs. In addition, the German data include prescriptions that are reimbursed via private insurance schemes, potentially including a wider selection of drugs. Overall, the ability to study CAPs authorized for < 2 years is limited but the experience of 3 months of PRAC meetings has shown that only six recent substances (of 128 in total) were discussed by the PRAC over the 3-month period. Although we looked at *all* medicines discussed at PRAC over a 3-month period, it should be noted that there was a potential role for the analysis of EHR analysis in supporting PRAC decision making in only a minority of cases. However, the purpose of our analysis was to establish the applicability of available data to the sorts of drug that are, in general, discussed at PRAC, rather than to imply that each of the medicines listed required additional analysis.

The use of EHDs seems able to address safety concerns for most medicines if the adverse event of interest is in the common or very common categories. Adverse events of such frequencies may already be well characterized by prelicensing and postlicensing randomized trials, and the role of EHRs to provide further data may be limited to addressing the frequency and characteristics of events in real-world use. It is for adverse events that are less common (those that are uncommon, rare, or very rare in frequency), or adverse events that only appear after long-term treatment or which have a long latency period, where primary EHDs would be most informative. We found that for CAPs in particular, only a minority of medicinal substances being discussed by the PRACs had sufficient data to allow meaningful comparison of event rates between the exposure of interest and a comparator cohort. As might be expected for primary care databases, coverage was lower for medicinal products that were more likely to be used in a secondary or tertiary care setting. Primary EHDs are key data sources to provide information on use and effects of medicines in routine clinical practice, but our study highlights the need for regulators to supplement them with data sources that include medicines used prescribed in specialized settings.

The relevance of a database for particular research depends on the question to be addressed. Exploring this Coloma *et al.* used data from eight European databases to determine the amount of drug exposure required for signal detection across varying

Table 5 Number and percentages of NAP substances discussed by PRAC (n = 45) for which a causal association with a suspected ADR could be investigated according to different background rates and strengths of association

Background risk	Association with RR of 2.0		Association of RR of 4.0	
(per number of patients)	Required[a] number of patients exposed	No (%: 95% confidence interval) of substances that can be investigated	Required[a] number of patients	No (%: 95% confidence interval) of substances that can be investigated
Very common (< 1/10)	282	FR: 27 (60.0: 45.5–73.0) DE: 32 (71.1: 56.6–82.3) UKTh: 30 (66.7: 52.1–78.6) UKCP: 30 (66.7: 52.1–78.6) All: 37 (82.2: 68.7–90.7)	47	FR: 29 (64.4: 49.8–76.8) DE: 36 (80.0: 66.2–89.1) UKTh: 31 (68.9: 54.3–80.5) UKCP: 31 (68.9: 54.3–80.5) All: 40 (88.9: 76.5–95.2)
Common (1/100)	3,220	FR: 23 (51.1: 37.0–65.0) DE: 26 (57.8: 43.3–71.0) UKTh: 26 (57.8: 43.3–71.0) UKCP: 27 (60.0: 45.5–73.0) All: 33 (73.3: 59.0–84.0)	585	FR: 26 (57.8: 43.3–71.0) DE: 31 (68.9: 54.3–80.5) UKTh: 29 (64.4: 49.8–76.8) UKCP: 29 (64.4: 49.8–76.8) All: 36 (80.0: 66.2–89.1)
Uncommon (1/1,000)	32,601	FR: 12 (26.7: 16.0–41.0) DE: 21 (46.7: 32.9–60.9) UKTh: 22 (48.9: 35.0–63.0) UKCP: 22 (48.9: 35.0–63.0) All: 27 (60.0: 45.5–73.0)	5,960	FR: 22 (48.9: 35.0–63.0) DE: 25 (55.6: 41.2–69.1) UKTh: 26 (57.8: 43.3–71.0) UKCP: 26 (57.8: 43.3–71.0) All: 32 (71.1: 56.6–82.3)
Rare (1/10,000)	326,417	FR: 2 (4.4: 1.2–14.8) DE: 6 (13.3: 6.3–26.2) UKTh: 11 (24.4: 14.2–38.7) UKCP: 11 (24.4: 14.2–38.7) All: 18 (40.0: 27.0–54.5)	59,708	FR: 8 (17.8: 9.3–31.3) DE: 19 (42.2: 29.0–56.7) UKTh: 21 (46.7: 32.9–60.9) UKCP: 21 (46.7: 32.9–60.9) All: 26 (57.8: 43.3–71.0)
Very rare (1/100,000)	3,264,571	FR: 0 (0.0: 0.0–7.9) DE: 0 (0.0: 0.0–7.9) UKTh: 0 (0.0: 0.0–7.9) UKCP: 1 (2.2: 0.4–11.6) All: 5 (11.1: 4.8–23.5)	597,186	FR: 1 (2.2: 0.4–11.6) DE: 5 (11.1: 4.8–23.5) UKTh: 8 (17.8: 9.3–31.3) UKCP: 8 (17.8: 9.3–31.3) All: 13 (28.9: 17.7–43.4)

ADR, adverse drug reaction; All, pooled data; CAP, centrally authorized products; DE, Germany; FR, France; IMRD, IQVIA Medical Research Data; PRAC, Pharmacovigilance Risk Assessment Committee; RR, relative risk; UKCP, Clinical Practice Research Datalink; UKTh, IMRD-United Kingdom.
[a]Based on a hypothetical comparison of two proportions using a two-sided Fisher exact test with $\alpha = 0.05$, power = 0.90 and equal numbers of patients exposed in the drug of interest and comparator cohorts.

magnitudes of RR. This calculation provided estimates of the number and types of drugs that can be monitored as a function of actual use, minimal detectable RR, and empirically derived incidence rates for six adverse events.[24] Based on drug exposure already available in the databases, they concluded that the leverage to perform active surveillance using healthcare data-based networks for signal detection is low for infrequently used drugs and for rare outcomes. In this evaluation, we took the real-life perspective of regulators needing or requiring investigations for drugs where there is no prior information on exposure in the databases.

Our study has some limitations. First, we chose three PRAC meetings for this evaluation in which 128 substances were discussed: 83 CAPs and 45 NAPs. An evaluation over a longer time period (for example, 1 year) in which a larger number of potentially different medicines were considered might provide different results. However, the discussion of issues by the PRAC is guided by aspects linked to the scientific assessment of medicinal products rather than by their characteristics, such as therapeutic class. Analyses also considered the authorization status (CAP/NAP) and duration of authorization. There is, therefore, no strong reason to believe that a longer or another period would give significantly different results. Second, the number of prescriptions and patients were estimated at any time in the lifecycle of the database until August 31, 2018, in order to reflect initial analyses performed to evaluate the feasibility of a study on specific products. We did not apply criteria for inclusion of the practice or study-specific restrictions in terms of medical history, patient characteristics (e.g., age and sex) or exposure time windows.[25] Applying such decisions would sharply decrease the number of patients eligible to enter the study population. We, therefore, consider that our results represent an "optimistic" view of the relevance of EHDs for analyses of substances discussed by PRAC. Third, we used the numbers of prescriptions as a proxy for exposure and the number of exposed patients rather than the amount of patient-time of exposure to determine the density of exposure to each concerned substance in the databases. In fact, the numbers of prescriptions and patients are the measures used in initial feasibility analyses as they do not require assumptions of duration of prescriptions and exposure time windows.[25] Fourth, **Tables 4 and 5**, describing the number of patient exposures required for different event rates and different RRs, were required to be simplistic and intended to be indicative only. Many potential factors can impact on a study's sample size calculation and, given limited space, we were only able to consider a limited number of scenarios. Other study designs would result in different sample size calculations and it should be noted that smaller RRs in particular—the likes of which are commonly encountered

when considering the safety of medicines—would require greater numbers to allow a meaningful analysis. Finally, we did not give consideration to the regulatory context outside Europe or to databases held outside Europe as this was thought to be outside the scope of our study.

Primary EHDs are a unique resource of information on the use of medicines in the community. This study has shown that to be of use to regulatory bodies, such as PRAC and EMA, they may need to be complemented by other data sources for some types of products and especially CAPs that may be prescribed by specialists. Such alternative datasets may be associated with their own limitations. Claims databases may cover an entire population in a region or country but contain less medical information on indication for treatments and possible clinical outcomes of these treatments. Record linkage systems allow the possibility of combining a wealth of data relating to prescriptions, clinical information, and hospital records typically based on a pseudo-anonymized deterministic patient identifier. However, much secondary care prescribing is not captured electronically and the pooling of several databases in this way raises other concerns, for example, those relating to data protection, and the potential to identify and compile data on individual patients. Solutions to such issues exist, for example, the Information Governance frameworks that exist in Scandinavia and elsewhere in the UK sources, but these can make access to such data more restrictive and limit the potential output of any analyses. The use of multidatabase networks (possibly incorporating the use of a common data model) has been advocated,[10,21–23] but there is currently no system that allows easy and rapid in-house access to such networks in Europe. It should be noted that the three countries contributing to our analysis (France, Germany, and the United Kingdom) have a greater number of medicinal products available, have some of the shortest times between authorization and active marketing, and have some of the best availability of both orphan and oncologic therapies in the European Union.[26] Interestingly, all three counties have well-established Health Technology Assessment procedure and it is reassuring to note that this results in high early uptake of newly authorized medicines.

In conclusion, this work assessed the extent to which medicinal substances discussed at PRAC over a 3-month period was covered in three in-house and one well-established third-party primary care databases. We found NAPs were better covered than CAPs, presumably because the latter tend to be more advanced therapies, which are typically administered in a specialized rather than a primary care setting. Newer medicinal substances were less well covered, as were medicinal substances for orphan conditions. To enable better informed regulatory decisions on the safety of medicines, the capture of patient-level secondary care prescribing should be a priority in the future. Regulators should consider using a range of data sources collecting data from different settings to capture a comprehensive picture of the use of medicines in clinical practice.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Supplemental Table. List of substances or classes of substances included in study.

FUNDING

No funding was received for this work.

CONFLICT OF INTEREST

All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

R.F., K.H., T.M.-T., A.P., P.A., H.S., P.M., and X.K. wrote the manuscript. R.F., K.H., T.M.-T., A.P., P.M., and X.K. designed the research. R.F., K.H., T.M.-T., and H.S. performed the research. R.F., K.H., and T.M.-T. analyzed the data.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies with which the authors are employed.

1. European Medicines Agency. Pharmacovigilance Risk Assessment Committee (PRAC) <https://www.ema.europa.eu/en/committees/pharmacovigilance-risk-assessment-committee-prachttps://www.ema.europa.eu/en/committees/pharmacovigilance-risk-assessment-committee-prac> (2019). Accessed August 22, 2019.
2. Santoro, A., Genov, G., Spooner, A., Raine, J. & Arlett, P. Promoting and protecting public health: how the European Union pharmacovigilance system works. *Drug Saf.* **40**, 855–869 (2017).
3. Cave, A., Kurz, X. & Arlett, P. Real-world data for regulatory decision making: challenges and possible solutions for Europe. *Clin. Pharmacol. Ther.* **106**, 36–39 (2019).
4. Hedenmalm, K. *et al*. A European multicentre drug utilisation study of the impact of regulatory measures on prescribing of codeine for pain in children. *Pharmacoepidemiol. Drug Saf.* **28**, 1086–1096 (2019).
5. Morales, D., Pacurariu, A., Slattery, J., Pinheiro, L., McGettigan, P. & Kurz, X. Association between peripheral neuropathy and exposure to oral fluoroquinolone or amoxicillin-clavulanate therapy. *JAMA Neurol.* **76**, 827–833 (2019).
6. Hedenmalm, K., Kurz, X. & Morales, D. Effect of withdrawal of fusafungine from the market on prescribing of antibiotics and other alternative treatments in Germany: a pharmacovigilance impact study. *Eur. J. Clin. Pharmacol.* **75**, 979–984 (2019).
7. Hedenmalm, K., Slattery, J., Skibicka-Stepien, I., Kurz, X. & Morales, D. Prescribing patterns of tramadol in adults in IMS® primary care databases in France and Germany between 1 January 2006 and 30 June 2016. *Eur. J. Clin. Pharmacol.* **75**, 707–716 (2019).
8. Morales, D., Slattery, J., Pacurariu, A., Pinheiro, L., McGettigan, P. & Kurz, X. Relative and absolute risk of tendon rupture with fluoroquinolone and concomitant fluoroquinolone/corticosteroid therapy: population-based nested case-control study. *Clin. Drug. Investig.* **39**, 205–213 (2019).
9. Morales, D., Flynn, R. & Kurz, X. Addendum to: relative and absolute risk of tendon rupture with fluoroquinolone and concomitant fluoroquinolone/corticosteroid therapy: population-based nested case-control study. *Clin. Drug Investig.* **39**, 591–594 (2019).

10. Schneeweiss, S. & Avorn, J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J. Clin. Epidemiol.* **58**, 323–337 (2005).
11. Coloma, P.M. *et al*. Electronic healthcare databases for active drug safety surveillance: is there enough leverage? *Pharmacoepidemiol. Drug Saf.* **21**, 611–621 (2012).
12. European Medicines Agency. Annual report 2018 <https://www.ema.europa.eu/en/documents/annual-report/2018-annual-report-european-medicines-agency_en.pdf> (2019). Accessed August 22, 2019.
13. Barkholt, L., Voltz-Girolt, C., Raine, J., Salmonson, T. & Schüssler-Lenz, M. European regulatory experience with advanced therapy medicinal products. *Nat. Rev. Drug Discov.* **18**, 8–9 (2019).
14. McGettigan, P. *et al*. Patient registries: an underused resource for medicines evaluation: operational proposals for increasing the use of patient registries in regulatory assessments. *Drug Saf.* **42**, 1343–1351 (2019).
15. Arlett, P. *et al*. Proactively managing the risk of marketed drugs: experience with the EMA Pharmacovigilance Risk Assessment Committee. *Nat. Rev. Drug Discov.* **13**, 395–397 (2014).
16. European Medicine Agency. Public data from Article 57 database <www.ema.europa.eu> (2019). Accessed August 26, 2019.
17. NHS Digital. Prescription Cost Analysis (PCA)-England, 2018 <https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018> (2019). Accessed August 26, 2019.
18. L'Assurance Maladie. Medic'AM mensuel: janvier à décembre 2018 <https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques> (2019). Accessed August 26, 2019.
19. PharMaAnalyst. Auswertung aller Verordnungsdaten der Gesetzlichen Krankenversicherung (GKV), 2018 <https://arzneimittel.wido.de/PharMaAnalyst> (2019). Accessed August 26, 2019.
20. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2019 <https://www.whocc.no/atc_ddd_index/> (2019) Accessed August 26, 2019.
21. Pacurariu, A. *et al*. Electronic healthcare databases in Europe: descriptive analysis of characteristics and potential for use in medicines regulation. *BMJ Open*. **8**, e023090 (2018).
22. Erikssen, I. & Ibanez, L. Secondary data sources for drug utilization research. In *Drug Utilization Research: Methods and Applications* (eds. Elseviers, M. *et al*.) 39-48 (John Wiley & Sons, Chichester, 2016).
23. Hall, G., Sauer, B., Bourke, A., Brown, J., Reynolds, M. & LoCasale, R. Guidelines for good database selection and use in pharmacoepidemiology research. *Pharmacoepidemiol. Drug Saf.* **21**, 1–10 (2012).
24. Coloma, P.M. *et al*. Electronic healthcare databases for active drug safety surveillance: is there enough leverage? *Pharmacoepidemiol. Drug Saf.* **21**, 611–621 (2012).
25. Wang, S.V. *et al*. Reporting to improve reproducibility and facilitate validity assessment for healthcare database studies V1.0. *Pharmacoepidemiol. Drug Saf.* **26**, 1018–1032 (2017).
26. European Federation of Pharmaceutical Industries and Associations Document. EFPIA Patient W.A.I.T. Indicator 2018 survey <https://www.efpia.eu/media/412747/efpia-patient-wait-indicator-study-2018-results-030419.pdf> (2019). Accessed December 18, 2019.