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Impact of real world evidence on medicines regulation in the European Union: a systematic assessment of European Medicines Agency referrals 2013-2017

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Abstract

Objectives: To assess the use, and evaluate the usefulness, of non-interventional studies and routinely collected healthcare data in post-marketing assessments conducted by the European Medicines Agency (EMA).

Design: We reviewed and systematically assessed all referrals to the EMA made due to safety or efficacy concerns that were evaluated between 1st January 2013 and 30th June 2017. We extracted information from the assessment report and the referral notification. Two reviewers independently assessed the contribution of non-interventional evidence to decision-making.

Results: The preliminary evidence leading to the assessment in 52 eligible referrals was mostly from spontaneous reports (cited in 26 of 52 referrals) and randomised trials (22/52). In contrast, many evidence types were used for the full assessment. Non-interventional studies were frequently used in the full assessment for the evaluation of product safety (31/52) and product efficacy (18/52). In particular, non-interventional studies were relied upon for the evaluation of safety and efficacy in subgroups, the evaluation of safety relating to a rare adverse event, understanding product usage and misuse, and for evaluation of the effectiveness of risk minimisation measures. The most common recommendations were changes to product information (43/52) and marketing authorisation withdrawal or suspension (12/52). In the majority of referrals non-interventional evidence was judged to contribute to the decision made (30/52) and in 3 referrals it was the primary source of evidence.

Conclusions: European regulatory decision-making relies on multiple evidence types, particularly randomised trials, spontaneous reports and non-interventional studies. Non-interventional studies had an important role particularly for the characterisation and quantification of adverse events, the

evaluation of product usage, and for evaluating the effectiveness of regulatory action to minimise risk.

Keywords: real world evidence, non-interventional studies, medicines regulation

Strengths and limitations of this study

- We assessed all safety and efficacy post-marketing authorisation referrals completed through the European Medicines Agency (EMA) between January 2013 and June 2017. Previous studies focused on marketing authorisation withdrawal only, but we included referrals regardless of referral outcome.

- While previous studies investigated which different evidence types are used in regulatory decision-making, these did not look in depth at the role of these different evidence types, and in particular at the role of non-interventional evidence, which we examined in detail.

- Though the majority of studies cited in the referral assessment reports could be identified, occasionally referencing was incomplete and there was insufficient detail to determine basic study information.

- Judgement on the role of non-interventional evidence in each assessment was to some extent subjective and is dependent of what is recorded in the assessment report. However, close agreement between two independent reviewers was observed.

Introduction

There is an ongoing public debate about the use of routinely collected healthcare data in research, particularly regarding concerns over patient confidentiality.[1 2] Conducting research that meets strict confidentiality requirements is of paramount importance, but for public trust to be established and maintained there is also a need for evidence that research using patient records provides clear benefits for the wider public. One potentially important and generally agreed benefit is in evaluating the safety of drugs in real world use, though surprisingly, there is no comprehensive and systematic evidence of how data from patient records is currently used in this context, with previous summaries focussing largely on safety assessments resulting in marketing authorisation withdrawal or suspension.[3-11]

Real world evidence has been defined in a number of ways. The US 21st Century Cures Act defines it as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional trials". [12] An alternative definition of real world evidence, is evidence derived from information collected for purposes other than research (i.e. routinely collected healthcare data such as electronic healthcare records and insurance claims data).[13] Whilst this evidence can be generated by (pragmatic) randomised clinical trials, currently non-interventional studies are the predominant source of real-world evidence, and these are the focus of our study.[13 14]

Regulatory authorities increasingly require non-interventional evidence of drug effects. As a result of the US 21st Century Cures Act, the US Food and Drug Administration (FDA) is developing a framework for the use of non-randomised "real world evidence" in the approval of new indications and in post-authorisation medicinal product assessment.[12] Similarly the European Medicines Agency's (EMA) adaptive pathway approach forms a new route of approval for medicines, allowing conditional approval in areas of unmet need, subject to further evidence collection, particularly of non-randomised real world evidence.[15] EU legislation also now mandates the assessment of medication effectiveness in routine clinical care where warranted.[16] The focus on using non-

interventional data to evaluate the expected effectiveness of medicines is relatively new; agreed methodologies and experience are limited.

The aim of this study was to systematically assess the type of evidence used in post-authorisation drug regulation by the European Medicines Agency (EMA) to give a better understanding of the contribution of non-interventional evidence and routinely collected data in this setting.

Methods

We identified and reviewed all EMA post-marketing authorisation referrals made for safety and/or efficacy concerns which were evaluated by an assessment committee between 1st January 2013 and 30th June 2017. The EMA is the European Union (EU) agency responsible for the scientific evaluation, supervision, and safety monitoring of medicines used in the EU. Its work includes the evaluation of applications for marketing authorisation and the monitoring of approved medicines. We evaluated referrals which concluded after 2012 since EU legislation on pharmacovigilance was strengthened in that year. The evaluated referrals were made in accordance with the directives of European Parliament: Article 107(i) of Directive 2001/83/EC, Article 31 of Directive 2001/83/EC, and Article 20 of Regulation No 726/2004 (supplementary appendix A – table 1).

When an EU member state or the European Commission has a significant concern regarding the safety or efficacy of an approved medicine, a referral process is initiated. The EMA initially publishes a notification which details the reasons for the referral. The safety and/or efficacy of the medicine is then assessed in depth by designated member states and subsequently evaluated by one or more of the EMA committees which include the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee for Medicinal Products for Human Use (CHMP), and the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). Finally, an assessment report is published by the EMA for each referral, providing information on the recommendations made by the assessment committee and the reasons for these recommendations.

Eligible referrals were identified from the EMA website. One reviewer (JPB) evaluated the notification and assessment report of each referral using a form (supplementary appendix B). Information was extracted about the notification, the referral, the medicinal product, the adverse events under study, and the types of evidence assessed (pre-clinical, non-randomised trials, randomised trials, non-interventional studies, spontaneous reports and systematic reviews). In addition, the reviewer assessed how different study types were used within the referral process and

categorised usage into: mechanism of action, pharmacokinetics/pharmacodynamics, efficacy, risk, product usage, and the effectiveness of risk minimisation measures.

For each referral the adverse events under study were recorded and categorised into their respective Medical Dictionary for Regulatory Activities (MedDRA) system organ class.[17] Drugs were categorised by Anatomical Therapeutic Chemical (ATC) classification system code.[18]

Two reviewers (JPB and IJD) independently assessed the recommendations made in the assessment report, and the contribution of non-interventional studies to the recommendation made, with disagreements resolved through discussion. We aimed to determine whether evidence from non-interventional studies, and in particular, non-interventional studies using routinely collected data, had an important or pivotal role in the assessment, in order to determine the contribution of this type of evidence in this context.

Patient involvement

No patients were involved in the development of the research question, definition of study outcomes or study design. We will disseminate our study findings to patients through social media and using patient groups with an interest in data.

Results

Referrals

Sixty potentially eligible referrals were identified with a committee opinion date between 1st January 2013 and the 31st June 2017. Of these 60 referrals, 8 were excluded, either because they related to bioequivalence (n=4) or manufacturing concerns (n=3) rather than safety/efficacy concerns, or because an assessment report was not yet available as of the 31st October 2017 (n=1).

The most frequent initiators of referrals were the European Commission (n=13), France (n=12), the UK (n=8), Germany (n=4) and Italy (n=4). According to the referral notification and assessment report, 21 of 52 referrals (40%) were made due to a combination of safety and efficacy concerns, 29 (56%) due to safety concerns only, and 2 (4%) due to efficacy concerns only.

Drug groups and adverse events

The most common drug groups defined according to ATC code were sex hormones and modulators of the genital system, and analgesics (6 referrals each), followed by drugs used in diabetes, cough and cold preparations, anti-inflammatory and anti-rheumatic products, and cardiac therapies (3 referrals each) (supplementary appendix A - table 2). The most common body systems on which referred products acted were, based on ATC code, the nervous system (n=13), the cardiovascular system (n=9), the alimentary tract and metabolism (n=8), and the genitourinary system and sex hormones (n=8) (supplementary appendix A - table 3).

The most commonly investigated adverse events included arterial thromboembolism (n=5), venous thromboembolism (n=4), hypersensitivity (n=4) and renal impairment (n=3). The most frequent category of adverse events according to MedDRA system organ class were cardiac and vascular disorders (n=16); nervous system disorders (n=15); respiratory, thoracic and mediastinal disorders (n=7); and skin and subcutaneous tissue disorders (n=7) (supplementary appendix A - table 4).

Evidence usage

Evidence cited by the initial notification and the referral assessment report was categorised by type (table 1). Where no notification was available (in 12 of 52 referrals) information on the evidence leading to the referral was extracted from the EMA website and the assessment report. The evidence leading to referral was most commonly spontaneous reports (50%, 26/52) and randomised trials (42%, n=22). Assessment reports also frequently cited spontaneous reports (73%, n=38) and randomised trials (92%, n=48), but frequently cited non-interventional studies (79%, n=41) too. Among the 52 referrals, in the assessment report, 31 (60%) cited non-interventional studies using pre-existing routinely collected data (e.g. electronic medical records) and 33 (63%) cited non-interventional studies using data collected specifically for research. Evidence was also frequently cited from non-randomised trials (63%, 33/52), preclinical studies (56%, n=29) and systematic reviews of randomised trials (52%, n=27). The quality of study description and referencing varied considerably by assessment report. It was not always possible to find a corresponding study publication or to ascertain the design for every study mentioned in the assessment; 63% (33/52) of assessment reports referred to at least one study of unclear design.

Table 2 summarises how each type of evidence contributed to different aspects of the assessments. The efficacy of medications was largely determined through evidence from randomised trials (cited with regard to efficacy in 77% (40/52) of referrals), with non-interventional studies contributing information on efficacy in 25% (13/52) of assessments. Non-interventional studies contributed to the assessment of efficacy, to a limited degree, and mostly when clinical trial data was limited, such as in a subgroup (e.g. hydroxyethyl starch in trauma patients - EMEA/H/A-107i/1376; intravenous nicardipine in children and pregnant women - EMEA/H/A-31/1339), for a product developed prior to current regulatory requirements (e.g. polymyxin - EMEA/H/A-31/1383), or where a clinical trial would be difficult to run due to sporadic and unpredictable need for therapy (e.g. adrenaline auto-injectors - EMEA/H/A-31/1398; methysergide for cluster headache - EMEA/H/A-31/1335).

For overall risks, both randomised trials (69%, 36/52) and non-interventional studies (60%, n=31) were commonly assessed, alongside evidence from spontaneous reports (71%, n=37). Product usage, where assessed, was almost entirely assessed based on non-interventional evidence (27%, n=14). Mechanistic evidence was largely obtained from pre-clinical sources (31%, n=16), whilst pharmacokinetics and pharmacodynamics were addressed through non-randomised trials (19%, n=10), randomised trials (19%, n=10) and pre-clinical studies (12%, n=6).

Investigation of product usage and misuse was almost entirely based on non-interventional data (table 2). Non-interventional evidence was also cited for estimating background incidence rates of the adverse event in the population, and for characterising the prevalence of additional risk factors and effect modifiers for the outcome under study.

Role of non-interventional evidence

Over half of the assessments relied at least in part on evidence from non-interventional studies to be able to make recommendations for regulatory action (e.g. MA suspension or change in product information) (table 3). Only in 11 of 52 assessments (21%) were no non-interventional studies cited. In a further 11 referrals non-interventional studies were cited, but the reports did not indicate that they contributed significantly to the decision made, either because only a few pertinent non-interventional studies were cited (n=9), or due to limitations of the non-interventional studies (n=2).

In three referrals (combined hormonal contraceptives and thromboembolism; valproate, birth defects and developmental disorders (EMEA/H/A-31/1387); and Kogenate Bayer/Helixate NexGen and factor VIII inhibition (EMEA/H/C/275/A20/150/ EMEA/H/C/276/A20/143) non-interventional studies alone were the primary source of evidence. When stratified by the outcome of the assessment, it appears that non-interventional evidence more often contributed to decision-making in referrals leading to prescribing changes (64%, 27/42) than those leading to suspension (33%,

4/12), though only 12 assessments led to suspension or withdrawal of marketing authorisation (table 3).

Non-interventional studies were of particular use for the evaluation of safety in a subpopulation who were largely or completely excluded from clinical trials, such as pregnant women. They were also vital for estimating the risk of rare adverse outcomes, such as venous thromboembolism with oral contraceptives, for which clinical trials were underpowered. Relative to spontaneous reports, non-interventional studies were particularly useful when reporting was strongly influenced by the media, such as with human papillomavirus (HPV) vaccines (EMEA/H/A-20/1421), and when the outcome was unlikely to be picked up by case reports, such as exposure-outcome associations with a long latency period (e.g. Caustinerf arsenical and cancer (EMEA/H/A-31/1382)). Non-interventional studies using routinely collected data were mostly used in a similar way to studies using data collected for research (table 2). Studies using routinely collected data were particularly useful when the outcome was rare, whereas studies using data collected for research purposes were most useful where the outcome was poorly recorded in clinical records (e.g. Numeta G13%E/G16%E and hypermagnesemia - EMEA/H/A-107i/1373).

Referral outcomes

The majority (98%, 51/52) of referrals led to regulatory action, with the assessment committee recommending changes to the product information (83%, n=43) and particularly changes to the warnings, posology, undesirable effects and indication sections of the Summary of Product Characteristics (table 4). In 12 of 52 (23%) referrals suspension or withdrawal of marketing authorisation was recommended. Only for one referral into the safety of HPV vaccines was no change recommended.

For many referrals (42%, n=22) the assessment committee required further specific studies to be conducted, generally to elucidate safety, product usage and the effectiveness of risk minimisation

measures. From a review of the assessment reports and the EU register of post-authorisation studies (EU PAS register) most of these were non-interventional studies using routinely collected data or data collected for research purposes (required in 19 referrals).

Discussion

In this comprehensive evaluation, we have shown that a wide range of evidence sources are used to aid decision making during EU drug regulatory referrals. The three types cited in the majority of assessments were randomised trials, spontaneous reports and non-interventional studies. Although non-interventional evidence is rarely cited in notifications leading to a referral, it is cited substantially during the detailed assessment of most issues, and in a few referrals was the primary evidence type used in decision-making. Notably, at the end of an assessment when recommendations were made for evidence gaps to be filled, further non-interventional evidence was required more often than any other type.

Each type of evidence appears to contribute to different aspects of a drug safety/efficacy referral, allowing for a well-rounded assessment of medication risks and benefits. Unsurprisingly, given their unique inferential advantages, randomised trials are relied on more than any other evidence type to provide evidence of drug efficacy. Current usage of non-interventional evidence for efficacy largely occurs where clinical trial data are limited. Increasingly, however, regulators require measures of drug effectiveness in routine clinical care, for which well-designed non-interventional studies and pragmatic clinical trials using routinely collected data could be highly informative.[12 15 16]

To assess safety issues non-interventional evidence is heavily relied on alongside randomised trials and spontaneous reports. Although less frequently cited, evidence from sources such as pre-clinical studies is occasionally relied on to provide information about mechanisms of effect or pharmacokinetics/pharmacodynamics.

Strengths and Limitations

We were able to assess almost all referrals completed between 2013 and 2017, making this the most comprehensive summary of recent drug regulatory decision making. The assessment reports are a

comprehensive summary of the evidence used in decision making, meaning we were able to determine how each type of evidence contributed to the final recommendations.

We were unable to directly assess the quality and validity of individual studies included in the assessments. However, by reviewing the assessment reports, we evaluated how the evidence had been rated by the committees and how it had contributed to the overall decisions made. Occasionally studies were mentioned in assessment reports but no reference to a publication was given, or referencing was incomplete, and there was insufficient detail for readers to determine basic information such as the study design or setting.

Judgement about how evidence was used in an assessment is to some extent subjective and is also reliant on what is recorded in each assessment report. However, close agreement was achieved between the two reviewers in this study.

Previous studies of the role of different evidence types in drug regulatory decision making have largely focused on marketing authorisation withdrawals/suspensions.[3-11] These studies highlight how the balance of evidence types has shifted over time, from heavy reliance on spontaneous reports to a more comprehensive reliance on varied evidence types. Over a similar time period the overall number of non-interventional studies conducted and published also appears to be increasing, with studies of UK electronic primary care data a prime example of this trend.[19] With the increase in research opportunities provided by new database linkages this publication trend is likely to continue.

Unique strengths of non-interventional evidence

Non-interventional evidence was mostly used to inform on safety issues. Certain aspects of a safety assessment appear to benefit from the availability of non-interventional evidence, such as the quantification of rare events, investigation of special populations (e.g. pregnant women and children), and informing about drug usage patterns. Whilst other types of evidence are also useful in some of these areas, our study highlighted occasions when non-interventional evidence is unique

and vital for regulatory decision making. The risk of developmental disability and birth defects in the offspring of women taking valproate in pregnancy is a key example of this.[20] This rare outcome occurring in a group largely excluded from randomised trials could not have been characterised and quantified without large, well-powered non-interventional studies. Similarly, the detailed characterisation and quantification of adverse outcomes associated with NSAIDs and the oral contraceptive could not have been done without good quality non-interventional evidence. Where media interest led to stimulated spontaneous reporting, such as in the case of HPV vaccine and various adverse effects, unbiased evidence from non-interventional settings was vital in providing reassurance of safety, enabling continued use of the vaccine with no further action required. Randomised trials used to justify licensing of medicines are simply too small to detect even relatively common adverse reactions. The median number of patients studied on a new active substance is 1,708 for standard medicines and 438 for orphan medicines in the European Union[21]. Rare adverse reactions (such as those occurring in 1 in 500 patients) will not have been detected as caused by the medicine, but such rare effects can dramatically alter the benefit/risk balance of the medicine.

Tellingly, where the EMA's committees call for further studies to be done, they mostly require non-interventional evidence. There is increasingly a recognition that regulatory action to minimise risks needs to be followed up to determine how effective it has been.[22] Almost all drug regulatory action involves making changes to how medicines are used in routine clinical care, and to determine whether new directives are being followed requires evidence obtained in the routine clinical care setting. Patterns of drug usage and quantification or characterisation of adverse events following regulatory action are often required; non-interventional studies will be most important here, and though spontaneous reports may also be useful, they are mostly unable to give quantitative information.

There are three key elements required to ensure a successful future for non-interventional evidence within the framework of drug regulatory science. First, there are legitimate concerns regarding the

use of evidence from non-interventional studies in drug regulation given the potential problems of missing data and residual confounding.[23] Through high quality study design, conduct and reporting these issues can in many cases be resolved[24]. Secondly, timely evidence is needed; non-interventional studies can be conducted rapidly in response to emerging issues, or to measure the effectiveness of past regulatory action. Thirdly, the data used in non-interventional studies needs to be of the highest standard. This includes both the quality of the data and its generalisability to the population from which it comes. Data quality can be monitored and assured by data custodians.[25] Generalisability relies on research data being drawn from a representative sample of the population. Whether data are taken from existing medical records or newly collected for a specific study, this requires the majority of patients to consent to their data to be included. For such a transaction between researchers and patients to operate successfully, maintaining anonymity and confidentiality is paramount.

Conclusions

Regulatory decision making about the safety and efficacy of medication in the European Union relies on evidence obtained from a wide range of sources; most frequently from randomised trials, spontaneous reports and non-interventional studies. Non-interventional evidence can be vital for characterising and quantifying adverse drug reactions, is often needed for monitoring the effectiveness of regulatory action to minimise risks, and in certain situations will be the only available evidence.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: JPB had financial support from ABPI for the submitted work; IJD has received a grant from the ABPI for the study in question, financial support from GlaxoSmithKline for work unrelated to the study in question, has consulted for GlaxoSmithKline and Gilead, and holds stock in GlaxoSmithKline; SE is an independent European Commission-appointed expert member of EMA's PRAC; LS reports personal fees from GSK outside the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work. The views expressed in this article are personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Author contributions: All authors were involved in the design of the study. JPB and IJD undertook the data collection and drafted the manuscript. All authors interpreted the results, contributed to later drafts of the manuscript, and approved the final manuscript.

Data sharing: All data analysed is available publically on the European Medicines Agency (https://www.ema.europa.eu/) and EU Register of Post-Authorisation Studies (http://www.encepp.eu/) websites.

Patient consent: Not required.

Ethics approval: Not required.

Tables

Table 1: Evidence leading to referral and evidence cited in assessment report for the 52 included referrals

	Evidence leading to referral[a]		In assessment report	
Type of evidence	**Number of referrals**	**% of all referrals**	**Number of referrals**	**% of all referrals**
Pre-clinical evidence	4	8%	29	56%
Non - randomised trials	1	2%	33	63%
Randomised trials	22	42%	48	92%
Non-interventional studies	13	25%	41	79%
i. Using routinely collected data	8	15%	31	60%
ii. Using data collected for research	6	12%	33	63%
Spontaneous reports	26	50%	38	73%
Systematic review of randomised trials	7	13%	27	52%
Systematic review of non-interventional studies	1	2%	4	8%
Systematic review combining randomised trials & non-interventional studies	0	0%	8	15%
Unclear	11	21%	33	63%

a. This was primarily based on the referral notification. However, for 12 of 52 referrals no notification was available and evidence leading to initiation was instead obtained from the assessment report and from the description of the referral on the EMA website.

Table 2: Number and percentage of all referrals (n=52) that use each type of evidence for each purpose

Type of evidence	Usage[a]						
	Mechanism	PK/PD[b]	Efficacy	Risk - Overall	Risk - subgroup	Usage of product	Effectiveness of risk minimisation measures
Pre-clinical evidence	16 (31%)	6 (12%)	2 (4%)	10 (19%)	1 (2%)	0 (0%)	0 (0%)
Non - randomised trials	1 (2%)	10 (19%)	18 (35%)	14 (27%)	2 (4%)	0 (0%)	0 (0%)
Randomised trials	3 (6%)	9 (17%)	40 (77%)	36 (69%)	7 (13%)	0 (0%)	1 (2%)
Non-interventional	3 (6%)	4 (8%)	18 (35%)	31 (60%)	5 (10%)	14 (27%)	0 (0%)
Non-interventional using routinely collected data	0 (0%)	1 (2%)	8 (15%)	25 (48%)	4 (8%)	10 (19%)	0 (0%)
Non-interventional using data collected for research	2 (4%)	4 (8%)	13 (25%)	20 (38%)	3 (6%)	7 (13%)	0 (0%)
Spontaneous reports	2 (4%)	0 (0%)	3 (6%)	37 (71%)	6 (12%)	4 (8%)	0 (0%)
Systematic review of randomised trials	0 (0%)	0 (0%)	19 (37%)	10 (19%)	1 (2%)	0 (0%)	0 (0%)
Systematic review of non-interventional studies	0 (0%)	0 (0%)	0 (0%)	4 (8%)	1 (2%)	0 (0%)	0 (0%)
Systematic review of randomised trials & non-interventional studies	0 (0%)	1 (2%)	2 (4%)	4 (8%)	0 (0%)	0 (0%)	0 (0%)
Unclear study design	1 (2%)	8 (15%)	12 (23%)	10 (19%)	0 (0%)	1 (2%)	0 (0%)

a. Usage was categorised, as detailed in the table, into: mechanism of adverse event with product usage, pharmacokinetics/pharmacodynamics of product, efficacy of product, risk of adverse events with product, risk of adverse events with product in a subpopulation, usage/misuse of a product, and effectiveness of regulatory risk minimisation measures.
b. Pharmacokinetics/pharmacodynamics

Table 3: Usage of non-interventional studies in referral assessment reports

Usage of non-interventional studies	All referrals (n=52)		Referrals leading to MA withdrawal/suspension (n=12)		Referrals leading to changes to product information (n=43)	
	Number of referrals	% of all referrals	Number of referrals	% of all referrals	Number of referrals	% of all referrals
No evidence from non-interventional studies was cited in the report	11	21%	4	33%	7	16%
Evidence from non-interventional studies was cited, but made little to no contribution to the decision	11	21%	4	33%	9	21%
The decision was consistent with evidence from non-interventional studies, and also consistent with other evidence	27	52%	4	33%	24	56%
The decision was consistent with evidence from non-interventional studies AND this evidence was the primary or only factor involved in the decision e.g. there was some spontaneous reports and some large non-interventional studies	3	6%	0	0%	3	7%

Table 4: Recommendations made as a result of assessment for the 52 included referrals

Recommendation	Number of referrals	% of all referrals
No change	1	2%
Further evidence before decision-making	2	4%
Suspension or withdrawal of marketing authorisation	12	23%
Change to product information	43	83%
By section of the Summary of Product Characteristics:		
- Indication	24	46%
- Posology	28	54%
- Contraindications	22	42%
- Warnings	39	75%
- Interactions	14	27%
- Pregnancy	10	19%
- Driving/machinery	2	4%
- Undesirable effects	26	50%
- Overdose	3	6%
- Studies	13	25%
- Nature and contents	3	6%

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Supplementary Appendix A

Table 1: EMA referrals categorised by type and date

Referral category	Frequency by CHMP/CMDh opinion date					Total
	2013	2014	2015	2016	2017 Jan-Jun	
Article 107i procedures	5	1	0	0	0	6
Article 20 procedures	2	3	1	4	1	11
Article 31 referrals	13	13	5	3	1	35
Total	20	17	6	7	2	52

Table 2: ATC therapeutic subgroups by frequency for the 52 included referrals

ATC subgroup code	Subgroup definition	No. of referrals
G03	Sex hormones and modulators of the genital system	6
N02	Analgesics	6
A10	Drugs used in diabetes	3
C01	Cardiac therapy	3
M01	Anti-inflammatory and antirheumatic products	3
None	Not applicable/available	3
R05	Cough and cold preparations	3
A03	Drugs for functional gastrointestinal disorders	2
B05	Blood substitutes and perfusion solutions	2
C04	Peripheral vasodilators	2
C10	Lipid modifying agents	2
G02	Other gynelogicals	2
L01	Antineoplastic agents	2
M03	Muscle relaxants	2
N05	Psycholeptics	2
R03	Drugs for obstructive airway diseases	2
B01	Antithrombotic agents	1
B02	Antihemorrhagics	1
B03	Antianemic preparations	1
C08	Calcium channel blockers	1
C09	Agents acting on the renin-angiotensin system	1
J01	Antibacterials for systemic use	1
J02	Antimycotics for systemic use	1
J05	Antivirals for systemic use	1
L04	Immunosuppresants	1
M05	Drugs for treatment of bone diseases	1
N03	Antiepileptics	1
N07	Psychoanaleptics	1
R02	Throat preparations	1
R07	Other respiratory system products	1

Table 3: ATC section by frequency for the 52 included referrals

ATC section	Section definition	Number of referrals
N	Nervous system	13
C	Cardiovascular system	9
A	Alimentary tract and metabolism	8
G	Genitourinary system and sex hormones	8
R	Respiratory system	7
M	Musculoskeletal system	6
B	Blood and blood forming organs	5
J	Anti-infectives for systemic use	3
L	Antineoplastic and immunomodulating agents	3
D	Dermatologicals	0
H	Systemic hormonal preparations, excluding sex hormones and insulins	0
P	Antiparasitic products, insecticides and repellents	0
S	Sensory organs	0
V	Various	0

Table 4: MedDRA system organ class (SOC) of adverse event by frequency for the 52 included referrals

System Organ Class (SOC)	Number of referrals
Cardiac disorders	16
Vascular disorders	15
Nervous system disorders	9
Respiratory, thoracic and mediastinal disorders	7
Skin and subcutaneous tissue disorders	7
Gastrointestinal disorders	6
Immune system disorders	5
Infections and infestations	5
Renal and urinary disorders	5
Blood and lymphatic system disorders	4
Hepatobiliary disorders	4
Metabolism and nutrition disorders	4
Neoplasms benign, malignant and unspecified	4
Congenital, familial and genetic disorders	2
Endocrine disorders	2
Musculoskeletal and connective tissue disorders	2
Injury, poisoning and procedural complications	1
Reproductive system and breast disorders	1
Sexual function and fertility disorders	1
Surgical and Medical Procedures	1

Supplementary Appendix B: Data collection form

1. Basic information about referral	EMA reference number	
	Initiated by (e.g. MHRA, European Commission)	
	Referral/procedure type	(Article 107i/Article 31/Article 20)
	Decision making model (e.g. PRAC-EC)	
	Cause of referral	(Safety/Efficacy/Safety and efficacy)
	Cause of referral – description	
	CHMP opinion/CMDh position date	
2. Information about product and adverse event	Review title	
	Substance name	
	Product usage	
	ATC group (e.g. N03 - Antiepileptics)	
	Product class (as listed on EMA website)	
	Adverse events	
	MedDRA system organ classes of adverse events	
3. Determine the types of evidence leading to the referral	Source of evidence	(Notification/Assessment report/EMA webpage)
	a. Pre-clinical evidence	(Yes/No/Unclear)
	b. Non-randomised trials	(Yes/No/Unclear)
	c. Randomised trials	(Yes/No/Unclear)
	d. Observational studies	(Yes/No/Unclear)
	i. Using routinely collected real world data e.g. electronic health records	(Yes/No/Unclear)
	ii. Using primary data collection e.g. pregnancy registry	(Yes/No/Unclear)
	e. Spontaneous reports	(Yes/No/Unclear)
	f. Systematic review of randomised trials	(Yes/No/Unclear)

	g. Systematic review of observational studies	(Yes/No/Unclear)
	h. Systematic review combining randomised trials & observational studies	(Yes/No/Unclear)
	i. Unclear design	(Yes/No)
4. a) Determine the types of evidence used in each assessment report	a. Pre-clinical evidence	(Yes/No/Unclear)
	b. Non-randomised trials	(Yes/No/Unclear)
	c. Randomised trials	(Yes/No/Unclear)
	d. Observational studies	(Yes/No/Unclear)
	i. Using routinely collected real world data e.g. electronic health records	(Yes/No/Unclear)
	ii. Using primary data collection e.g. pregnancy registry	(Yes/No/Unclear)
	e. Spontaneous reports	(Yes/No/Unclear)
	f. Systematic review of randomised trials	(Yes/No/Unclear)
	g. Systematic review of observational studies	(Yes/No/Unclear)
	h. Systematic review combining randomised trials & observational studies	(Yes/No/Unclear)
	i. Unclear design	(Yes/No)
4. b) Summarise the types of evidence used in each assessment report	a. Pre-clinical evidence	
	b. Non - randomised trials	
	c. Randomised trials	
	d. Observational studies	
	e. Spontaneous reports	
	f. Systematic review of clinical trials	
	g. Systematic review of observational studies	
	h. Systematic review combining clinical trials & observational studies	
	i. Unclear design	

5. Determine the recommendation made in the report.	a. No change – the available evidence dismisses any concern	(Yes/No)
	b. Further evidence before decision-making	(Yes/No)
	c. Change to product information e.g. restriction of use, addition of new adverse drug reaction, restriction of dose etc.	(Yes/No)
	d. Change to availability e.g. P to POM	(Yes/No)
	e. Suspension or revocation of marketing authorisation	(Yes/No)
	Summary of decision	

6. If there was a recommendation for a change to product information, which sections of the summary of product characteristics (SmPc) were affected?	4.1 Therapeutical indications	
	4.2 Posology and method of administration	
	4.3 Contraindications	
	4.4 Special warnings and precautions for use	
	4.5 Interactions with other medicinal products and other forms of interaction	
	4.6 Fertility, pregnancy and lactation	
	4.7 Effects on ability to drive and use machines	
	4.8 Undesirable effects	
	4.9 Overdose	
	Other	

7. Determine how observational studies contributed to the decision made. Judgement is involved in this step and the assessment will be conducted independently by two researchers.	(a. No evidence from observational studies was cited in the report/ b. Evidence from observational studies was cited, but made little to no contribution to the decision/ c. Evidence from observational studies was cited, but the decision was contrary to this evidence/ d. The decision was consistent with evidence from observational studies, and also consistent with other evidence/ e. The decision was consistent with evidence from observational studies AND this evidence was the primary or only factor involved in the decision/ f. Unclear)
8. What was useful (or otherwise) about the evidence from observational studies?	

9. If no observational studies were available, were such studies feasible and could they have been useful?	Yes/no?	(Yes/No/Unclear)
	Further information	
10. Does the action taken as a result of the referral require future research?	Yes/no?	(Yes/No/Unclear)
	Is further non-interventional evidence required?	(Yes/No/Unclear)
	Further information	
	Design of further non-interventional studies in PAS register	(using data collected for research/ using routinely collected data)

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Use of real world evidence in post-marketing medicines regulation in the European Union: a systematic assessment of European Medicines Agency referrals 2013-2017

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Abstract

Objectives: To assess the use, and evaluate the usefulness, of non-interventional studies and routinely collected healthcare data in post-marketing assessments conducted by the European Medicines Agency (EMA).

Design: We reviewed and systematically assessed all referrals to the EMA made due to safety or efficacy concerns that were evaluated between 1st January 2013 and 30th June 2017. We extracted information from the assessment report and the referral notification. Two reviewers independently assessed the contribution of non-interventional evidence to decision-making.

Results: The preliminary evidence leading to the assessment in 52 eligible referrals was mostly from spontaneous reports (cited in 26 of 52 referrals) and randomised trials (22/52). In contrast, many evidence types were used for the full assessment. Non-interventional studies were frequently used in the full assessment for the evaluation of product safety (31/52) and product efficacy (18/52). In particular, non-interventional studies were relied upon for the evaluation of safety and efficacy in subgroups, the evaluation of safety relating to a rare adverse event, understanding product usage and misuse, and for evaluation of the effectiveness of risk minimisation measures. The most common recommendations were changes to product information (43/52) and marketing authorisation withdrawal or suspension (12/52). In the majority of referrals non-interventional evidence was judged to contribute to the decision made (30/52) and in 3 referrals it was the primary source of evidence.

Conclusions: European regulatory decision-making relies on multiple evidence types, particularly randomised trials, spontaneous reports and non-interventional studies. Non-interventional studies had an important role particularly for the characterisation and quantification of adverse events, the

evaluation of product usage, and for evaluating the effectiveness of regulatory action to minimise risk.

Keywords: real world evidence, non-interventional studies, medicines regulation

Strengths and limitations of this study

- We assessed all safety and efficacy post-marketing authorisation referrals completed through the European Medicines Agency (EMA) between January 2013 and June 2017. Previous studies focused on marketing authorisation withdrawal only, but we included referrals regardless of referral outcome.
- While previous studies investigated which different evidence types are used in regulatory decision-making, these did not look in depth at the role of these different evidence types, and in particular at the role of non-interventional evidence, which we examined in detail.
- Though the majority of studies cited in the referral assessment reports could be identified, occasionally referencing was incomplete and there was insufficient detail to determine basic study information.
- Judgement on the role of non-interventional evidence in each assessment was to some extent subjective and is dependent of what is recorded in the assessment report. However, close agreement between two independent reviewers was observed.

Introduction

There is an ongoing public debate about the use of routinely collected healthcare data in research, particularly regarding concerns over patient confidentiality.[1 2] Conducting research that meets strict confidentiality requirements is of paramount importance, but for public trust to be established and maintained there is also a need for evidence that research using patient records provides clear benefits for the wider public. One potentially important and generally agreed benefit is in evaluating the safety of drugs in real world use, though surprisingly, there is no comprehensive and systematic evidence of how data from patient records is currently used in this context, with previous summaries focussing largely on safety assessments resulting in marketing authorisation withdrawal or suspension.[3-11]

Real world evidence has been defined in a number of ways. The US 21st Century Cures Act defines it as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional trials". [12] An alternative definition of real world evidence, is evidence derived from information collected for purposes other than research (i.e. routinely collected healthcare data such as electronic healthcare records and insurance claims data).[13] Whilst this evidence can be generated by (pragmatic) randomised controlled trials, currently non-interventional studies are the predominant source of real-world evidence, and these are the focus of our study.[13 14]

Regulatory authorities increasingly require non-interventional evidence of drug effects. As a result of the US 21st Century Cures Act, the US Food and Drug Administration (FDA) is developing a framework for the use of non-randomised "real world evidence" in the approval of new indications and in post-authorisation medicinal product assessment.[12 15] Similarly the European Medicines Agency's (EMA) adaptive pathway approach forms a new route of approval for medicines, blurring the lines between pre and post-marketing data collection, it seeks to facilitate conditional approval in areas of unmet need, subject to further evidence collection, particularly of non-randomised real world evidence.[16] EU legislation now mandates the assessment of medication effectiveness in

routine clinical care where warranted.[17] The focus on using non-interventional data to evaluate the expected effectiveness of medicines is relatively new; there are concerns over their validity to measure causal associations, and agreed methodologies and experience are limited.

The aim of this study was to systematically assess the type of evidence used in post-authorisation drug regulation by the European Medicines Agency (EMA) to give a better understanding of the contribution of non-interventional evidence and routinely collected data in this setting.

Methods

We identified and reviewed all EMA post-marketing authorisation referrals made for safety and/or efficacy concerns which were evaluated by an assessment committee between 1st January 2013 and 30th June 2017. The EMA is the European Union (EU) agency responsible for the scientific evaluation, supervision, and safety monitoring of medicines used in the EU. Its work includes the evaluation of applications for marketing authorisation and the monitoring of approved medicines. We evaluated referrals which concluded after 2012 since EU medicines regulation changed that year with legislation strengthening pharmacovigilance through many measures including the introduction of a Pharmacovigilance Risk Assessment Committee and increased regulatory requirements.[18] The evaluated referrals were made in accordance with the directives of European Parliament: Article 107(i) of Directive 2001/83/EC, Article 31 of Directive 2001/83/EC, and Article 20 of Regulation No 726/2004 (online supplementary table 1).

When an EU member state or the European Commission has a significant concern regarding the safety or efficacy of an approved medicine, a referral process is initiated. The EMA initially publishes a notification which details the reasons for the referral. The safety and/or efficacy of the medicine is then assessed in depth by designated member states and subsequently evaluated by one or more of the EMA committees which include the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use (CHMP), and the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). Finally, an assessment report is published by the EMA for each referral, providing information on the recommendations made by the assessment committee and the reasons for these recommendations.

Eligible referrals were identified from the EMA website. One reviewer (JPB) evaluated the notification and assessment report of each referral using a form (available in the online supplementary appendix). Information was extracted about the notification, the referral, the medicinal product, the adverse events under study, and the types of evidence assessed (pre-clinical,

non-randomised trials, randomised trials, non-interventional studies, spontaneous reports and systematic reviews; definitions in online supplementary appendix). In addition, the reviewer assessed how different study types were used within the referral process and categorised usage into: mechanism of action, pharmacokinetics/pharmacodynamics, efficacy, risk, product usage, and the effectiveness of risk minimisation measures (see the online supplementary appendix for an example). The referral outcome was categorised into: no change, further evidence before decision-making, suspension or withdrawal of marketing authorisation, change to availability, and change to product information (or a combination of these categories).

For each referral the adverse events under study were recorded and categorised into their respective Medical Dictionary for Regulatory Activities (MedDRA) system organ class.[19] Drugs were categorised by Anatomical Therapeutic Chemical (ATC) classification system code.[20]

Two reviewers (JPB and IJD) independently assessed the recommendations made in the assessment report, and judged the extent to which non-interventional studies were both cited and contributed to the recommendation made, with disagreements resolved through discussion. We aimed to determine whether evidence from non-interventional studies, and in particular, non-interventional studies using routinely collected data, had an important or pivotal role in the assessment, in order to determine the contribution of this type of evidence in this context.

Patient involvement

No patients were involved in the development of the research question, definition of study outcomes or study design. We will disseminate our study findings to patients through social media and using patient groups with an interest in data.

Results

Referrals

Sixty potentially eligible referrals were identified with a committee opinion date between 1st January 2013 and the 31st June 2017. Of these 60 referrals, 8 were excluded, either because they related to bioequivalence (n=4) or manufacturing concerns (n=3) rather than safety/efficacy concerns, or because an assessment report was not yet available as of the 31st October 2017 (n=1) (full list of included referrals included in the online supplementary appendix).

The most frequent initiators of referrals were the European Commission (n=13), France (n=12), the UK (n=8), Germany (n=4) and Italy (n=4). According to the referral notification and assessment report, 21 of 52 referrals (40%) were made due to a combination of safety and efficacy concerns, 29 (56%) due to safety concerns only, and 2 (4%) due to efficacy concerns only.

Drug groups and adverse events

The most common drug groups defined according to ATC code were sex hormones and modulators of the genital system, and analgesics (6 referrals each), followed by drugs used in diabetes, cough and cold preparations, anti-inflammatory and anti-rheumatic products, and cardiac therapies (3 referrals each) (online supplementary table 2). The most common body systems on which referred products acted were, based on ATC code, the nervous system (n=13), the cardiovascular system (n=9), the alimentary tract and metabolism (n=8), and the genitourinary system and sex hormones (n=8) (online supplementary table 3).

The most commonly investigated adverse events included arterial thromboembolism (n=5), venous thromboembolism (n=4), hypersensitivity (n=4) and renal impairment (n=3). The most frequent category of adverse events according to MedDRA system organ class were cardiac and vascular

disorders (n=16); nervous system disorders (n=15); respiratory, thoracic and mediastinal disorders (n=7); and skin and subcutaneous tissue disorders (n=7) (online supplementary table 4).

Evidence usage

Evidence cited by the initial notification and the referral assessment report was categorised by type (table 1). Where no notification was available (in 12 of 52 referrals) information on the evidence leading to the referral was extracted from the EMA website and the assessment report. The evidence leading to referral was most commonly spontaneous reports (50%, 26/52) and randomised trials (42%, n=22). Assessment reports also frequently cited spontaneous reports (73%, n=38) and randomised trials (92%, n=48), but frequently cited non-interventional studies (79%, n=41) too. Among the 52 referrals, in the assessment report, 31 (60%) cited non-interventional studies using pre-existing routinely collected data (e.g. electronic medical records) and 33 (63%) cited studies using data collected specifically for research. Evidence was also frequently cited from non-randomised trials (63%, 33/52), preclinical studies (56%, n=29) and systematic reviews of randomised trials (52%, n=27). The quality of study description and referencing varied considerably by assessment report. It was not always possible to find a corresponding study publication or to ascertain the design for every study mentioned in the assessment; 63% (33/52) of assessment reports referred to at least one study of unclear design.

Table 2 summarises how each type of evidence contributed to different aspects of the assessments. The efficacy of medications was largely determined through evidence from randomised trials (cited with regard to efficacy in 77% (40/52) of referrals), with non-interventional studies contributing information on efficacy in 25% (13/52) of assessments. Non-interventional studies contributed to the assessment of efficacy, to a limited degree, and mostly when clinical trial data was limited, such as in a subgroup (e.g. hydroxyethyl starch in trauma patients - EMEA/H/A-107i/1376; intravenous nicardipine in children and pregnant women - EMEA/H/A-31/1339), for a product developed prior to current regulatory requirements (e.g. polymyxin - EMEA/H/A-31/1383), or where a clinical trial

would be difficult to run due to sporadic and unpredictable need for therapy (e.g. adrenaline auto-injectors - EMEA/H/A-31/1398; methysergide for cluster headache - EMEA/H/A-31/1335).

For overall risks, both randomised trials (69%, 36/52) and non-interventional studies (60%, n=31) were commonly assessed, alongside evidence from spontaneous reports (71%, n=37). Product usage, where assessed, was almost entirely assessed based on non-interventional evidence (27%, n=14). Mechanistic evidence was largely obtained from pre-clinical sources (31%, n=16), whilst pharmacokinetics and pharmacodynamics were addressed through non-randomised trials (19%, n=10), randomised trials (19%, n=10) and pre-clinical studies (12%, n=6).

Investigation of product usage and misuse was almost entirely based on non-interventional data (table 2). Non-interventional evidence was also cited for estimating background incidence rates of the adverse event in the population, and for characterising the prevalence of additional risk factors and effect modifiers for the outcome under study.

Role of non-interventional evidence

Over half of the assessments relied at least in part on evidence from non-interventional studies to be able to make recommendations for regulatory action (e.g. MA suspension or change in product information) (table 3). Only in 11 of 52 assessments (21%) were no non-interventional studies cited. In a further 11 referrals non-interventional studies were cited, but the reports did not indicate that they contributed significantly to the decision made, either because only a few pertinent non-interventional studies were cited (n=9), or due to limitations of the non-interventional studies (n=2).

In three referrals (combined hormonal contraceptives and thromboembolism; valproate, birth defects and developmental disorders (EMEA/H/A-31/1387); and Kogenate Bayer/Helixate NexGen and factor VIII inhibition (EMEA/H/C/275/A20/150/ EMEA/H/C/276/A20/143) non-interventional studies alone were the primary source of evidence. When stratified by the outcome of the assessment, it appears that non-interventional evidence more often contributed to decision-making

in referrals leading to prescribing changes (64%, 27/42) than those leading to suspension (33%, 4/12), though only 12 assessments led to suspension or withdrawal of marketing authorisation (table 3).

Non-interventional studies were used for the evaluation of safety in a subpopulation who were largely or completely excluded from clinical trials, such as pregnant women. They were also used for estimating the risk of rare adverse outcomes, such as venous thromboembolism with oral contraceptives, for which clinical trials were underpowered. Relative to spontaneous reports, non-interventional studies contributed to decision-making more when reporting was strongly influenced by the media, such as with human papillomavirus (HPV) vaccines (EMEA/H/A-20/1421), and when the outcome was unlikely to be picked up by case reports, such as exposure-outcome associations with a long latency period (e.g. Caustinerf arsenical and cancer (EMEA/H/A-31/1382)). Non-interventional studies using routinely collected data were mostly used in a similar way to studies using data collected for research (table 2). Studies using routinely collected data were used more often when the outcome was rare, whereas studies using data collected for research purposes contributed more when the outcome was poorly recorded in clinical records (e.g. Numeta G13%E/G16%E and hypermagnesemia - EMEA/H/A-107i/1373).

Referral outcomes

The majority (98%, 51/52) of referrals led to regulatory action, with the assessment committee recommending changes to the product information (83%, n=43) and particularly changes to the warnings, posology, undesirable effects and indication sections of the Summary of Product Characteristics (table 4). In 12 of 52 (23%) referrals suspension or withdrawal of marketing authorisation was recommended. Only for one referral into the safety of HPV vaccines was no change recommended.

For many referrals (42%, n=22) the assessment committee required further specific studies to be conducted, generally to elucidate safety, product usage and the effectiveness of risk minimisation measures. From a review of the assessment reports and the EU register of post-authorisation studies (EU PAS register) most of these were non-interventional studies using routinely collected data or data collected for research purposes (required in 19 referrals).

Discussion

In this comprehensive evaluation, we have shown that a wide range of evidence sources are used to aid decision making during EU drug regulatory referrals. The three types cited in the majority of assessments were randomised trials, spontaneous reports and non-interventional studies. Although non-interventional evidence is rarely cited in notifications leading to a referral, it is cited substantially during the detailed assessment of most issues, and in a few referrals was the primary evidence type used in decision-making. Notably, at the end of an assessment when recommendations were made for evidence gaps to be filled, further non-interventional evidence was required more often than any other type.

Each type of evidence appears to contribute to different aspects of a drug safety/efficacy referral, allowing for a well-rounded assessment of medication risks and benefits. Unsurprisingly, given their unique inferential advantages, randomised trials are relied on more than any other evidence type to provide evidence of drug efficacy. Current usage of non-interventional evidence for efficacy largely occurs where clinical trial data are limited. Increasingly, however, regulators require measures of drug effectiveness in routine clinical care, for which well-designed non-interventional studies and pragmatic clinical trials using routinely collected data could be highly informative.[12 16 17]

To assess safety issues non-interventional evidence is heavily relied on alongside randomised trials and spontaneous reports. Although less frequently cited, evidence from sources such as pre-clinical studies is occasionally relied on to provide information about mechanisms of effect or pharmacokinetics/pharmacodynamics.

Strengths and Limitations

We were able to assess almost all referrals completed between 2013 and 2017, making this the most comprehensive summary of recent post-marketing drug regulatory decision making in Europe. The assessment reports are a comprehensive summary of the evidence used in decision making,

meaning we were able to determine how each type of evidence contributed to the final recommendations.

We were unable to directly assess the quality and validity of individual studies included in the assessments. However, by reviewing the assessment reports, we evaluated how the evidence had been rated by the committees and how it had contributed to the overall decisions made. Occasionally studies were mentioned in assessment reports but no reference to a publication was given, or referencing was incomplete, and there was insufficient detail for readers to determine basic information such as the study design or setting. More consistent and comprehensive referencing in assessment reports would increase the transparency of decision-making to the public and other stakeholders.

Judgement about how evidence was used in an assessment is to some extent subjective and is also reliant on what is recorded in each assessment report. However, close agreement was achieved between the two reviewers in this study.

Previous studies of the role of different evidence types in drug regulatory decision making have largely focused on marketing authorisation withdrawals/suspensions.[3-11 21] These studies highlight how the balance of evidence types has shifted over time, from heavy reliance on spontaneous reports to a more comprehensive reliance on varied evidence types including non-interventional studies, randomised controlled trials and meta-analyses. Over a similar time period the overall number of non-interventional studies conducted and published also appears to be increasing, with studies of UK electronic primary care data a prime example of this trend.[22] With the increase in research opportunities provided by new database linkages this publication trend is likely to continue.

Unique strengths of non-interventional evidence

Non-interventional evidence was particularly useful for the assessment of product safety in situations where evidence from randomised controlled trials was limited such as the quantification

of rare events, and the investigation of special populations (e.g. pregnant women and children). Whilst other types of evidence are also useful in some of these areas, our study highlighted occasions when non-interventional evidence is unique and vital for regulatory decision making. The risk of developmental disability and birth defects in the offspring of women taking valproate in pregnancy is a key example of this.[23] This rare outcome occurring in a group largely excluded from randomised trials could not have been characterised and quantified without large, well-powered non-interventional studies. Similarly, the detailed characterisation and quantification of adverse outcomes associated with NSAIDs and the oral contraceptive could not have been done without good quality non-interventional evidence. Where media interest led to stimulated spontaneous reporting, such as in the case of HPV vaccine and various adverse effects, unbiased evidence from non-interventional settings was vital in providing reassurance of safety, enabling continued use of the vaccine with no further action required. Randomised trials used to justify licensing of medicines are simply too small to detect even relatively common adverse reactions. The median number of patients studied on a new active substance is 1,708 for standard medicines and 438 for orphan medicines in the European Union[24]. Rare adverse reactions (such as those occurring in 1 in 500 patients) will not have been detected as caused by the medicine, but such rare effects can dramatically alter the benefit/risk balance of the medicine.

Where the EMA's committees call for further studies to be done, they frequently require non-interventional evidence. There is increasingly a recognition that regulatory action to minimise risks needs to be followed up to determine how effective it has been.[25] Almost all drug regulatory action involves making changes to how medicines are used in routine clinical care, and to determine whether new directives are being followed requires evidence obtained in the routine clinical care setting. Patterns of drug usage and quantification or characterisation of adverse events following regulatory action are often required; non-interventional studies will be important here, and though spontaneous reports may also be useful, they are mostly unable to give quantitative information.

There are three key elements required to ensure a successful future for non-interventional evidence within the framework of drug regulatory science. First, there are legitimate concerns regarding the use of evidence from non-interventional studies in drug regulation given the potential problems of missing data and residual confounding.[26] Through high quality study design, conduct and reporting these issues can in many cases be resolved[27]. Secondly, timely evidence is needed; non-interventional studies can be conducted rapidly in response to emerging issues, or to measure the effectiveness of past regulatory action. Thirdly, the data used in non-interventional studies needs to be of the highest standard. This includes both the quality of the data and its generalisability to the population from which it comes. Data quality can be monitored and assured by data custodians.[28] Generalisability relies on research data being drawn from a representative sample of the population. Whether data are taken from existing medical records or newly collected for a specific study, this requires the majority of patients to consent to their data to be included. For such a transaction between researchers and patients to operate successfully, maintaining anonymity and confidentiality is paramount.

Conclusions

Regulatory decision making about the safety and efficacy of medication in the European Union relies on evidence obtained from a wide range of sources; most frequently from randomised trials, spontaneous reports and non-interventional studies. Non-interventional evidence can be vital for characterising and quantifying adverse drug reactions, is often needed for monitoring the effectiveness of regulatory action to minimise risks, and in certain situations will be the only available evidence.

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Author contributions: IJD conceived the study. All authors (JPB, KW, SE, KB, LS, IJD) were involved substantially in the design and planning of the study. JPB and IJD undertook the data collection and wrote the initial draft of the manuscript. JPB conducted the data analyses. All authors interpreted the results, contributed to later drafts of the manuscript, and approved the final manuscript.

Data sharing: All data analysed is available publically on the European Medicines Agency (https://www.ema.europa.eu/) and EU Register of Post-Authorisation Studies (http://www.encepp.eu/) websites.

1 **Patient consent:** Not required.

2 **Ethics approval:** Not required.

Tables

Table 1: Evidence leading to referral and evidence cited in assessment report for the 52 included referrals

	Evidence leading to referral[a]		In assessment report	
Type of evidence	**Number of referrals**	**% of all referrals**	**Number of referrals**	**% of all referrals**
Pre-clinical evidence	4	8%	29	56%
Non - randomised trials	1	2%	33	63%
Randomised trials	22	42%	48	92%
Non-interventional studies	13	25%	41	79%
i. Using routinely collected data	8	15%	31	60%
ii. Using data collected for research	6	12%	33	63%
Spontaneous reports	26	50%	38	73%
Systematic review of randomised trials	7	13%	27	52%
Systematic review of non-interventional studies	1	2%	4	8%
Systematic review combining randomised trials & non-interventional studies	0	0%	8	15%
Unclear	11	21%	33	63%

a. This was primarily based on the referral notification. However, for 12 of 52 referrals no notification was available and evidence leading to initiation was instead obtained from the assessment report and from the description of the referral on the EMA website.

Table 2: Number and percentage of all referrals (n=52) that use each type of evidence for each purpose

Type of evidence	Usage[a]						
	Mechanism	PK/PD[b]	Efficacy	Risk - Overall	Risk - subgroup	Usage of product	Effectiveness of risk minimisation measures
Pre-clinical evidence	16 (31%)	6 (12%)	2 (4%)	10 (19%)	1 (2%)	0 (0%)	0 (0%)
Non - randomised trials	1 (2%)	10 (19%)	18 (35%)	14 (27%)	2 (4%)	0 (0%)	0 (0%)
Randomised trials	3 (6%)	9 (17%)	40 (77%)	36 (69%)	7 (13%)	0 (0%)	1 (2%)
Non-interventional	3 (6%)	4 (8%)	18 (35%)	31 (60%)	5 (10%)	14 (27%)	0 (0%)
Non-interventional using routinely collected data	0 (0%)	1 (2%)	8 (15%)	25 (48%)	4 (8%)	10 (19%)	0 (0%)
Non-interventional using data collected for research	2 (4%)	4 (8%)	13 (25%)	20 (38%)	3 (6%)	7 (13%)	0 (0%)
Spontaneous reports	2 (4%)	0 (0%)	3 (6%)	37 (71%)	6 (12%)	4 (8%)	0 (0%)
Systematic review of randomised trials	0 (0%)	0 (0%)	19 (37%)	10 (19%)	1 (2%)	0 (0%)	0 (0%)
Systematic review of non-interventional studies	0 (0%)	0 (0%)	0 (0%)	4 (8%)	1 (2%)	0 (0%)	0 (0%)
Systematic review of randomised trials & non-interventional studies	0 (0%)	1 (2%)	2 (4%)	4 (8%)	0 (0%)	0 (0%)	0 (0%)
Unclear study design	1 (2%)	8 (15%)	12 (23%)	10 (19%)	0 (0%)	1 (2%)	0 (0%)

Legend

Percentage of referrals that use evidence type for each purpose	Colour
<10%	
10-19%	
20-29%	
30-39%	
40%+	

a. Usage was categorised, as detailed in the table, into: mechanism of adverse event with product usage, pharmacokinetics/pharmacodynamics of product, efficacy of product, risk of adverse events with product, risk of adverse events with product in a subpopulation, usage/misuse of a product, and effectiveness of regulatory risk minimisation measures.
b. Pharmacokinetics/pharmacodynamics

Table 3: Usage of non-interventional studies in referral assessment reports

Usage of non-interventional studies	All referrals (n=52)		Referrals leading to MA[a] withdrawal/suspension (n=12)		Referrals leading to changes to product information (n=43)	
	Number of referrals	% of all referrals	Number of referrals	% of all referrals	Number of referrals	% of all referrals
No evidence from non-interventional studies was cited in the report	11	21%	4	33%	7	16%
Evidence from non-interventional studies was cited, but made little to no contribution to the decision	11	21%	4	33%	9	21%
The decision was consistent with evidence from non-interventional studies, and also consistent with other evidence	27	52%	4	33%	24	56%
The decision was consistent with evidence from non-interventional studies AND this evidence was the primary or only factor involved in the decision e.g. there was some spontaneous reports and some large non-interventional studies	3	6%	0	0%	3	7%

a. Marketing authorisation

Table 4: Recommendations made as a result of assessment for the 52 included referrals

Recommendation	Number of referrals	% of all referrals
No change	1	2%
Further evidence before decision-making	2	4%
Suspension or withdrawal of marketing authorisation	12	23%
Change to availability	0	0%
Change to product information	43	83%
By section of the Summary of Product Characteristics:		
- Indication	24	46%
- Posology	28	54%
- Contraindications	22	42%
- Warnings	39	75%
- Interactions	14	27%
- Pregnancy	10	19%
- Driving/machinery	2	4%
- Undesirable effects	26	50%
- Overdose	3	6%
- Studies	13	25%
- Nature and contents	3	6%

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Table 1: European Medicines Agency referrals categorised by type of referral procedure and date

Referral category	Frequency by CHMP/CMDh[a] opinion date					Total
	2013	2014	2015	2016	2017 Jan-Jun	
Article 107i procedures	5	1	0	0	0	6
Article 20 procedures	2	3	1	4	1	11
Article 31 referrals	13	13	5	3	1	35
Total	20	17	6	7	2	52

a) Committee for Medicinal Products for Human Use/Coordination Group for Mutual Recognition and Decentralised Procedures – Human

Table 2: ATC[a] therapeutic subgroup of medicinal product by frequency for the 52 included referrals

ATC subgroup code	Subgroup definition	No. of referrals
G03	Sex hormones and modulators of the genital system	6
N02	Analgesics	6
A10	Drugs used in diabetes	3
C01	Cardiac therapy	3
M01	Anti-inflammatory and antirheumatic products	3
None	Not applicable/available	3
R05	Cough and cold preparations	3
A03	Drugs for functional gastrointestinal disorders	2
B05	Blood substitutes and perfusion solutions	2
C04	Peripheral vasodilators	2
C10	Lipid modifying agents	2
G02	Other gynelogicals	2
L01	Antineoplastic agents	2
M03	Muscle relaxants	2
N05	Psycholeptics	2
R03	Drugs for obstructive airway diseases	2
B01	Antithrombotic agents	1
B02	Antihemorrhagics	1
B03	Antianemic preparations	1
C08	Calcium channel blockers	1
C09	Agents acting on the renin-angiotensin system	1
J01	Antibacterials for systemic use	1
J02	Antimycotics for systemic use	1
J05	Antivirals for systemic use	1
L04	Immunosuppresants	1
M05	Drugs for treatment of bone diseases	1
N03	Antiepileptics	1
N07	Psychoanaleptics	1
R02	Throat preparations	1
R07	Other respiratory system products	1

a) Anatomical Therapeutic Chemical (ATC) Classification System

Table 3: ATC[a] section of medicinal product by frequency for the 52 included referrals

ATC section	Section definition	Number of referrals
N	Nervous system	13
C	Cardiovascular system	9
A	Alimentary tract and metabolism	8
G	Genitourinary system and sex hormones	8
R	Respiratory system	7
M	Musculoskeletal system	6
B	Blood and blood forming organs	5
J	Anti-infectives for systemic use	3
L	Antineoplastic and immunomodulating agents	3
D	Dermatologicals	0
H	Systemic hormonal preparations, excluding sex hormones and insulins	0
P	Antiparasitic products, insecticides and repellents	0
S	Sensory organs	0
V	Various	0

a) Anatomical Therapeutic Chemical (ATC) Classification System

Table 4: MedDRA[a] system organ class (SOC) of adverse event by frequency for the 52 included referrals

System Organ Class (SOC)	Number of referrals
Cardiac disorders	16
Vascular disorders	15
Nervous system disorders	9
Respiratory, thoracic and mediastinal disorders	7
Skin and subcutaneous tissue disorders	7
Gastrointestinal disorders	6
Immune system disorders	5
Infections and infestations	5
Renal and urinary disorders	5
Blood and lymphatic system disorders	4
Hepatobiliary disorders	4
Metabolism and nutrition disorders	4
Neoplasms benign, malignant and unspecified	4
Congenital, familial and genetic disorders	2
Endocrine disorders	2
Musculoskeletal and connective tissue disorders	2
Injury, poisoning and procedural complications	1
Reproductive system and breast disorders	1
Sexual function and fertility disorders	1
Surgical and Medical Procedures	1

a) Medical Dictionary for Regulatory Activities

European Medicines Agency referrals included in the study

EMA[a] Reference No.	CHMP[b] opinion/CMDh[c] position date	Referral Title
EMEA/H/C/889/A20/37 EMEA/H/C/903/A20/38 EMEA/H/C/897/A20/38	17/01/2013	Tredaptive, Pelzont and Trevaclyn
EMEA/H/A-31/1306	21/03/2013	Cilostazol-containing medicines
EMEA/H/A107i/1352	24/04/2013	Tetrazepam-containing medicines
EMEA/H/A-107i/1357	29/05/2013	Cyproterone and ethinylestradiol containing medicinal products
EMEA/H/A-31/1346	29/05/2013	Almitrine-containing medicines
EMEA/H/A-107i/1363	26/06/2013	Flupirtine-containing medicines
EMEA/H/A-31/1342	26/06/2013	Codeine-containing medicines
EMEA/H/A-31/1344	26/06/2013	Diclofenac-containing medicines
EMEA/H/A-31/1325	27/06/2013	Ergot derivatives
EMEA/H/A-31/1322	27/06/2013	Intravenous iron-containing medicinal products
EMEA/H/A-31/1314	25/07/2013	Ketoconazole-containing medicines
EMEA/H/A-107i/1373	18/09/2013	Numeta G13E and Numeta G16E emulsion for infusion
EMEA/H/A-107i/1376	23/10/2013	Hydroxyethyl starch solutions for infusion
EMEA/H/A-31/1348	23/10/2013	Hydroxyethyl starch solutions for infusion
EMEA/H/A-31/1347	23/10/2013	Short-acting beta-agonists
EMEA/H/A-31/1339	24/10/2013	Intravenous nicardipine medicines
EMEA/H/A-31/1321	24/10/2013	Metoclopramide-containing medicines
EMA/H/A-31/1361	21/11/2013	Thiocolchicoside-containing medicines
EMEA/H/A-31/1366	18/12/2013	Substances related to nicotinic acid
EMEA/H/C/275/A20/150 EMEA/H/C/276/A20/143	19/12/2013	Kogenate Bayer and Helixate NexGen
EMEA/H/A-31/1356	16/01/2014	Combined hormonal contraceptives
EMEA/H/A20/1371/C/00560-561/0039-0034	20/02/2014	Protelos and Osseor
EMEA/H/A-31/1335	20/02/2014	Methysergide-containing medicines
EMEA/H/A-31/1349	19/03/2014	Diacerein-containing medicines for oral administration
EMEA/H/A-31/1365	24/04/2014	Domperidone-containing medicines
EMEA/H/A-31/1377	24/04/2014	Zolpidem-containing medicines
EMEA/H/A-31/1382	25/04/2014	Caustinerf arsenical and Yranicid arsenical
EMEA/H/A-31/1336	25/04/2014	Linoladiol N and Linoladiol HN
EMEA/H/A-31/1370	22/05/2014	Renin-angiotensin-system (RAS)-acting agents
EMEA/H/A-107i/1395	23/07/2014	Methadone medicinal products for oral use containing povidone
EMEA/H/A-31/1391	24/07/2014	Emergency contraceptives
EMEA/H/A-31/1379	20/08/2014	Bromocriptine-containing medicines indicated in the prevention or suppression of physiological lactation post-partum
EMEA/H/C/2695/A20/0003	23/10/2014	Iclusig
EMEA/H/A-31/1383	23/10/2014	Polymyxin-containing medicines
EMEA/H/A-31/1396	19/11/2014	Testosterone-containing medicines
EMEA/H/A-31/1387	19/11/2014	Valproate and related substances
EMEA/H/A20/1404/C/000598/0031 EMEA/H/A20/1404/C/000597/0032	20/11/2014	Corlentor and Procoralan
EMEA/H/A-31/1400	25/03/2015	Hydroxyzine-containing medicinal products

EMEA/H/A-31/1394	22/04/2015	Codeine-containing medicinal products for the treatment of cough or cold in paediatric patients
EMEA/H/A-31/1401	20/05/2015	Ibuprofen- and dexibuprofen-containing medicines
EMEA/H/A-31/1398	25/06/2015	Adrenaline auto-injectors
EMEA/H/A-31/1397	18/11/2015	Ambroxol and bromhexine-containing medicines
EMEA/H/A-20/1421	19/11/2015	Human papillomavirus vaccines
EMEA/H/A-20/1419	25/02/2016	SGLT2 (sodium-glucose co-transporter 2) inhibitors
EMEA/H/A-20/1416/C/000603/0083	25/02/2016	Tysabri
EMEA/H/A-31/1420	31/03/2016	Fusafungine containing medicinal products for oromucosal and nasal use
EMEA/H/A-31/1415	28/04/2016	Inhaled corticosteroids containing medicinal products indicated in the treatment of chronic obstructive pulmonary disease
EMEA/H/A-20/1439/C/3843/0023	21/07/2016	Zydelig
EMEA/H/A-31/1432	13/10/2016	Metformin and metformin-containing medicines
EMEA/H/A-20/1438	15/12/2016	Direct-acting antivirals indicated for treatment of hepatitis C (interferon-free)
EMEA/H/A-31/1435	26/01/2017	Dienogest/ethinylestradiol-containing medicinal products indicated in acne
EMEA/H/A-20/1442	23/02/2017	SGLT2 (sodium-glucose co-transporter 2) inhibitors (previously canagliflozin)

a) European Medicines Agency
b) Committee for Medicinal Products for Human Use
c) Coordination Group for Mutual Recognition and Decentralised Procedures – Human

Definition of key terms in study

Study type	Definition
Pre-clinical evidence	Evidence from in-vitro and in-vivo (non-human animals) experimentation.
Non-randomised trials	Interventional studies where assignment to therapy was not at random or where there was only one trial arm (e.g. Phase 1 and Phase 2 trials).
Randomised trials	Interventional studies where assignment to therapy versus control was random (including both traditional multi-arm randomised controlled trials and randomised crossover trials).
Interventional studies	Clinical studies where the study investigators intervene on patient therapy.
Non-interventional studies	Clinical studies where there is no intervention by study investigators. Alternatively termed observational studies.
Spontaneous reports	Unsolicited reports of adverse outcomes reported by consumers or healthcare professionals.

Primary Data collection form

1. Basic information about referral	EMA[a] reference number	
	Initiated by (e.g. MHRA[b], European Commission)	
	Referral/procedure type	(Article 107i/Article 31/Article 20)
	Decision making model (e.g. PRAC-CMDh-EC[c])	
	Cause of referral	(Safety/Efficacy/Safety and efficacy)
	Cause of referral – description	
	CHMP[d] opinion/CMDh[e] position date	
2. Information about product and adverse event	Review title	
	Substance name	
	Product usage	
	ATC[f] group (e.g. N03 - Antiepileptics)	
	Product class (as listed on EMA website)	
	Adverse events	
	MedDRA[g] system organ classes of adverse events	
3. Determine the types of evidence leading to the referral	Source of evidence	(Notification/Assessment report/EMA webpage)
	a. Pre-clinical evidence	(Yes/No/Unclear)
	b. Non-randomised trials	(Yes/No/Unclear)
	c. Randomised trials	(Yes/No/Unclear)
	d. Non-interventional studies	(Yes/No/Unclear)
	i. Using routinely collected real world data e.g. electronic health records	(Yes/No/Unclear)
	ii. Using primary data collection e.g. pregnancy registry	(Yes/No/Unclear)
	e. Spontaneous reports	(Yes/No/Unclear)
	f. Systematic review of randomised trials	(Yes/No/Unclear)

	g. Systematic review of non-interventional studies	(Yes/No/Unclear)
	h. Systematic review combining randomised trials & non-interventional studies	(Yes/No/Unclear)
	i. Unclear design	(Yes/No)
4. a) Determine the types of evidence used in each assessment report	a. Pre-clinical evidence	(Yes/No/Unclear)
	b. Non-randomised trials	(Yes/No/Unclear)
	c. Randomised trials	(Yes/No/Unclear)
	d. Non-interventional studies	(Yes/No/Unclear)
	i. Using routinely collected real world data e.g. electronic health records	(Yes/No/Unclear)
	ii. Using primary data collection e.g. pregnancy registry	(Yes/No/Unclear)
	e. Spontaneous reports	(Yes/No/Unclear)
	f. Systematic review of randomised trials	(Yes/No/Unclear)
	g. Systematic review of non-interventional studies	(Yes/No/Unclear)
	h. Systematic review combining randomised trials & non-interventional studies	(Yes/No/Unclear)
	i. Unclear design	(Yes/No)
4. b) Summarise the types of evidence used in each assessment report	a. Pre-clinical evidence	
	b. Non - randomised trials	
	c. Randomised trials	
	d. Non-interventional studies	
	e. Spontaneous reports	
	f. Systematic review of randomised trials	
	g. Systematic review of non-interventional studies	
	h. Systematic review combining randomised trials & non-interventional studies	
	i. Unclear design	

5. Determine the recommendation made in the report.	a. No change – the available evidence dismisses any concern	(Yes/No)
	b. Further evidence before decision-making	(Yes/No)
	c. Change to product information e.g. restriction of use, addition of new adverse drug reaction, restriction of dose etc.	(Yes/No)
	d. Change to availability e.g. P to POM	(Yes/No)
	e. Suspension or revocation of marketing authorisation	(Yes/No)
	Summary of decision	
6. If there was a recommendation for a change to product information, which sections of the summary of product characteristics (SmPc) were affected?	4.1 Therapeutical indications	
	4.2 Posology and method of administration	
	4.3 Contraindications	
	4.4 Special warnings and precautions for use	
	4.5 Interactions with other medicinal products and other forms of interaction	
	4.6 Fertility, pregnancy and lactation	
	4.7 Effects on ability to drive and use machines	
	4.8 Undesirable effects	
	4.9 Overdose	
	Other	
7. Determine how non-interventional studies contributed to the decision made. Judgement is involved in this step and the assessment will be conducted independently by two researchers.	(a. No evidence from non-interventional studies was cited in the report/ b. Evidence from non-interventional studies was cited, but made little to no contribution to the decision/ c. Evidence from non-interventional studies was cited, but the decision was contrary to this evidence/ d. The decision was consistent with evidence from non-interventional studies, and also consistent with other evidence/ e. The decision was consistent with evidence from non-interventional studies AND this evidence was the primary or only factor involved in the decision/ f. Unclear)	
8. What was useful (or otherwise) about the evidence from non-interventional studies?		

9. If no non-interventional studies were available, were such studies feasible and could they have been useful?	Yes/no?	(Yes/No/Unclear)
	Further information	
10. Does the action taken as a result of the referral require future research?	Yes/no?	(Yes/No/Unclear)
	Is further non-interventional evidence required?	(Yes/No/Unclear)
	Further information	
	Design of further non-interventional studies in PAS register	(using data collected for research/ using routinely collected data)

a) European Medicines Agency
b) Medicines and Healthcare Regulatory Agency
c) Pharmacovigilance Risk Assessment Committee – Coordination Group for Mutual Recognition and Decentralised Procedures (Human) - European Commission
d) Committee for Medicinal Products for Human Use
e) Coordination Group for Mutual Recognition and Decentralised Procedures – Human
f) Anatomical Therapeutic Chemical (ATC) Classification System

Secondary data collection form - Example

EMEA/H/A-107i/1395	Pre-clinical evidence	Non - randomised trials	Randomised trials	NI[a] studies	NI studies using RCD[b]	NI studies using primary data collection	Spontaneous reports	Systematic review of randomised trials	Systematic review of NI studies	Systematic review combining randomised trials & NI studies	Unclear study design
Mechanism of AE[c] with product	No	No	No	No	No	No	Yes	No	No	No	No
Pharmacokinetics/ Pharmacodynamics	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Efficacy	No	No	Yes	No	No	No	No	Yes	No	No	No
Risk - Overall	Yes	No	No	No	No	No	Yes	No	No	No	Yes
Risk - Subpopulation	No	No	No	No	No	No	No	No	No	No	No
Usage of product	No	No	No	Yes	Yes	Yes	No	No	No	No	No
Effectiveness of risk minimisation	No	No	No	No	No	No	No	No	No	No	No

a. Non-interventional studies
b. Routinely collected data
c. Adverse event

BMJ Open

Use of real world evidence in post-marketing medicines regulation in the European Union: a systematic assessment of European Medicines Agency referrals 2013-2017

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Use of real world evidence in post-marketing medicines regulation in the European Union: a systematic assessment of European Medicines Agency referrals 2013-2017

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Abstract

Objectives: To assess the use, and evaluate the usefulness, of non-interventional studies and routinely collected healthcare data in post-marketing assessments conducted by the European Medicines Agency (EMA).

Design: We reviewed and systematically assessed all referrals to the EMA made due to safety or efficacy concerns that were evaluated between 1st January 2013 and 30th June 2017. We extracted information from the assessment report and the referral notification. Two reviewers independently assessed the contribution of non-interventional evidence to decision-making.

Results: The preliminary evidence leading to the assessment in 52 eligible referrals was mostly from spontaneous reports (cited in 26 of 52 referrals) and randomised trials (22/52). In contrast, many evidence types were used for the full assessment. Non-interventional studies were frequently used in the full assessment for the evaluation of product safety (31/52) and product efficacy (18/52). In particular, non-interventional studies were relied upon for the evaluation of safety and efficacy in subgroups, the evaluation of safety relating to a rare adverse event, understanding product usage and misuse, and for evaluation of the effectiveness of risk minimisation measures. The most common recommendations were changes to product information (43/52) and marketing authorisation withdrawal or suspension (12/52). In the majority of referrals non-interventional evidence was judged to contribute to the decision made (30/52) and in 3 referrals it was the primary source of evidence.

Conclusions: European regulatory decision-making relies on multiple evidence types, particularly randomised trials, spontaneous reports and non-interventional studies. Non-interventional studies had an important role particularly for the characterisation and quantification of adverse events, the

evaluation of product usage, and for evaluating the effectiveness of regulatory action to minimise risk.

Keywords: real world evidence, non-interventional studies, medicines regulation

Strengths and limitations of this study

- We assessed all safety and efficacy post-marketing authorisation referrals completed through the European Medicines Agency (EMA) between January 2013 and June 2017. Previous studies focused on marketing authorisation withdrawal only, but we included referrals regardless of referral outcome.
- While previous studies investigated which different evidence types are used in regulatory decision-making, these did not look in depth at the role of these different evidence types, and in particular at the role of non-interventional evidence, which we examined in detail.
- Though the majority of studies cited in the referral assessment reports could be identified, occasionally referencing was incomplete and there was insufficient detail to determine basic study information.
- Judgement on the role of non-interventional evidence in each assessment was to some extent subjective and is dependent of what is recorded in the assessment report. However, close agreement between two independent reviewers was observed.

Introduction

There is an ongoing public debate about the use of routinely collected healthcare data in research, particularly regarding concerns over patient confidentiality.[1 2] Conducting research that meets strict confidentiality requirements is of paramount importance, but for public trust to be established and maintained there is also a need for evidence that research using patient records provides clear benefits for the wider public. One potentially important and generally agreed benefit is in evaluating the safety of drugs in real world use, though surprisingly, there is no comprehensive and systematic evidence of how data from patient records is currently used in this context, with previous summaries focussing largely on safety assessments resulting in marketing authorisation withdrawal or suspension.[3-14]

Real world evidence has been defined in a number of ways. The US 21st Century Cures Act defines it as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional trials". [15] An alternative definition of real world evidence, is evidence derived from information collected for purposes other than research (i.e. routinely collected healthcare data such as electronic healthcare records and insurance claims data).[16] Whilst this evidence can be generated by (pragmatic) randomised controlled trials, currently non-interventional studies are the predominant source of real-world evidence, and these are the focus of our study.[16 17]

Regulatory authorities increasingly require non-interventional evidence of drug effects. As a result of the US 21st Century Cures Act, the US Food and Drug Administration (FDA) is developing a framework for the use of non-randomised "real world evidence" in the approval of new indications and in post-authorisation medicinal product assessment.[15 18] Similarly the European Medicines Agency's (EMA) adaptive pathway approach forms a new route of approval for medicines, blurring the lines between pre and post-marketing data collection, it seeks to facilitate conditional approval in areas of unmet need, subject to further evidence collection, particularly of non-randomised real world evidence.[19] EU legislation now mandates the assessment of medication effectiveness in

routine clinical care where warranted.[20] The focus on using non-interventional data to evaluate the expected effectiveness of medicines is relatively new; there are concerns over their validity to measure causal associations, and agreed methodologies and experience are limited.

The aim of this study was to systematically assess the type of evidence used in post-authorisation drug regulation by the European Medicines Agency (EMA) to give a better understanding of the contribution of non-interventional evidence and routinely collected data in this setting.

Methods

We identified and reviewed all EMA post-marketing authorisation referrals made for safety and/or efficacy concerns which were evaluated by an assessment committee between 1st January 2013 and 30th June 2017. The EMA is the European Union (EU) agency responsible for the scientific evaluation, supervision, and safety monitoring of medicines used in the EU. Its work includes the evaluation of applications for marketing authorisation and the monitoring of approved medicines. We evaluated referrals which concluded after 2012 since EU medicines regulation changed that year with legislation strengthening pharmacovigilance through many measures including the introduction of a Pharmacovigilance Risk Assessment Committee and increased regulatory requirements.[21] The evaluated referrals were made in accordance with the directives of European Parliament: Article 107(i) of Directive 2001/83/EC, Article 31 of Directive 2001/83/EC, and Article 20 of Regulation No 726/2004 (online supplementary table 1).

When an EU member state or the European Commission has a significant concern regarding the safety or efficacy of an approved medicine, a referral process is initiated. The EMA initially publishes a notification which details the reasons for the referral. The safety and/or efficacy of the medicine is then assessed in depth by designated member states and subsequently evaluated by one or more of the EMA committees which include the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use (CHMP), and the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). Finally, an assessment report is published by the EMA for each referral, providing information on the recommendations made by the assessment committee and the reasons for these recommendations.

Eligible referrals were identified from the EMA website. One reviewer (JPB) evaluated the notification and assessment report of each referral using a form (available in the online supplementary appendix). Information was extracted about the notification, the referral, the medicinal product, the adverse events under study, and the types of evidence assessed (pre-clinical,

non-randomised trials, randomised trials, non-interventional studies, spontaneous reports and systematic reviews; definitions in online supplementary appendix). In addition, the reviewer assessed how different study types were used within the referral process and categorised usage into: mechanism of action, pharmacokinetics/pharmacodynamics, efficacy, risk, product usage, and the effectiveness of risk minimisation measures (see the online supplementary appendix for an example). The referral outcome was categorised into: no change, further evidence before decision-making, suspension or withdrawal of marketing authorisation, change to availability, and change to product information (or a combination of these categories).

For each referral the adverse events under study were recorded and categorised into their respective Medical Dictionary for Regulatory Activities (MedDRA) system organ class.[22] Drugs were categorised by Anatomical Therapeutic Chemical (ATC) classification system code.[23]

Two reviewers (JPB and IJD) independently assessed the recommendations made in the assessment report, and judged the extent to which non-interventional studies were both cited and contributed to the recommendation made, with disagreements resolved through discussion. We aimed to determine whether evidence from non-interventional studies, and in particular, non-interventional studies using routinely collected data, had an important or pivotal role in the assessment, in order to determine the contribution of this type of evidence in this context.

Patient involvement

No patients were involved in the development of the research question, definition of study outcomes or study design. We will disseminate our study findings to patients through social media and using patient groups with an interest in data.

Results

Referrals

Sixty potentially eligible referrals were identified with a committee opinion date between 1st January 2013 and the 31st June 2017. Of these 60 referrals, 8 were excluded, either because they related to bioequivalence (n=4) or manufacturing concerns (n=3) rather than safety/efficacy concerns, or because an assessment report was not yet available as of the 31st October 2017 (n=1) (full list of included referrals included in the online supplementary appendix).

The most frequent initiators of referrals were the European Commission (n=13), France (n=12), the UK (n=8), Germany (n=4) and Italy (n=4). According to the referral notification and assessment report, 21 of 52 referrals (40%) were made due to a combination of safety and efficacy concerns, 29 (56%) due to safety concerns only, and 2 (4%) due to efficacy concerns only.

Drug groups and adverse events

The most common drug groups defined according to ATC code were sex hormones and modulators of the genital system, and analgesics (6 referrals each), followed by drugs used in diabetes, cough and cold preparations, anti-inflammatory and anti-rheumatic products, and cardiac therapies (3 referrals each) (online supplementary table 2). The most common body systems on which referred products acted were, based on ATC code, the nervous system (n=13), the cardiovascular system (n=9), the alimentary tract and metabolism (n=8), and the genitourinary system and sex hormones (n=8) (online supplementary table 3).

The most commonly investigated adverse events included arterial thromboembolism (n=5), venous thromboembolism (n=4), hypersensitivity (n=4) and renal impairment (n=3). The most frequent category of adverse events according to MedDRA system organ class were cardiac and vascular

disorders (n=16); nervous system disorders (n=15); respiratory, thoracic and mediastinal disorders (n=7); and skin and subcutaneous tissue disorders (n=7) (online supplementary table 4).

Evidence usage

Evidence cited by the initial notification and the referral assessment report was categorised by type (table 1). Where no notification was available (in 12 of 52 referrals) information on the evidence leading to the referral was extracted from the EMA website and the assessment report. The evidence leading to referral was most commonly spontaneous reports (50%, 26/52) and randomised trials (42%, n=22). Assessment reports also frequently cited spontaneous reports (73%, n=38) and randomised trials (92%, n=48), but frequently cited non-interventional studies (79%, n=41) too. Among the 52 referrals, in the assessment report, 31 (60%) cited non-interventional studies using pre-existing routinely collected data (e.g. electronic medical records) and 33 (63%) cited studies using data collected specifically for research. Evidence was also frequently cited from non-randomised trials (63%, 33/52), preclinical studies (56%, n=29) and systematic reviews of randomised trials (52%, n=27). The quality of study description and referencing varied considerably by assessment report. It was not always possible to find a corresponding study publication or to ascertain the design for every study mentioned in the assessment; 63% (33/52) of assessment reports referred to at least one study of unclear design.

Table 2 summarises how each type of evidence contributed to different aspects of the assessments. The efficacy of medications was largely determined through evidence from randomised trials (cited with regard to efficacy in 77% (40/52) of referrals), with non-interventional studies contributing information on efficacy in 25% (13/52) of assessments. Non-interventional studies contributed to the assessment of efficacy, to a limited degree, and mostly when clinical trial data was limited, such as in a subgroup (e.g. hydroxyethyl starch in trauma patients - EMEA/H/A-107i/1376; intravenous nicardipine in children and pregnant women - EMEA/H/A-31/1339), for a product developed prior to current regulatory requirements (e.g. polymyxin - EMEA/H/A-31/1383), or where a clinical trial

would be difficult to run due to sporadic and unpredictable need for therapy (e.g. adrenaline auto-injectors - EMEA/H/A-31/1398; methysergide for cluster headache - EMEA/H/A-31/1335).

For overall risks, both randomised trials (69%, 36/52) and non-interventional studies (60%, n=31) were commonly assessed, alongside evidence from spontaneous reports (71%, n=37). Product usage, where assessed, was almost entirely assessed based on non-interventional evidence (27%, n=14). Mechanistic evidence was largely obtained from pre-clinical sources (31%, n=16), whilst pharmacokinetics and pharmacodynamics were addressed through non-randomised trials (19%, n=10), randomised trials (19%, n=10) and pre-clinical studies (12%, n=6).

Investigation of product usage and misuse was almost entirely based on non-interventional data (table 2). Non-interventional evidence was also cited for estimating background incidence rates of the adverse event in the population, and for characterising the prevalence of additional risk factors and effect modifiers for the outcome under study.

Role of non-interventional evidence

Over half of the assessments relied at least in part on evidence from non-interventional studies to be able to make recommendations for regulatory action (e.g. MA suspension or change in product information) (table 3). Only in 11 of 52 assessments (21%) were no non-interventional studies cited. In a further 11 referrals non-interventional studies were cited, but the reports did not indicate that they contributed significantly to the decision made, either because only a few pertinent non-interventional studies were cited (n=9), or due to limitations of the non-interventional studies (n=2).

In three referrals (combined hormonal contraceptives and thromboembolism; valproate, birth defects and developmental disorders (EMEA/H/A-31/1387); and Kogenate Bayer/Helixate NexGen and factor VIII inhibition (EMEA/H/C/275/A20/150/ EMEA/H/C/276/A20/143) non-interventional studies alone were the primary source of evidence. When stratified by the outcome of the assessment, it appears that non-interventional evidence more often contributed to decision-making

in referrals leading to prescribing changes (64%, 27/42) than those leading to suspension (33%, 4/12), though only 12 assessments led to suspension or withdrawal of marketing authorisation (table 3).

Non-interventional studies were used for the evaluation of safety in a subpopulation who were largely or completely excluded from clinical trials, such as pregnant women. They were also used for estimating the risk of rare adverse outcomes, such as venous thromboembolism with oral contraceptives, for which clinical trials were underpowered. Relative to spontaneous reports, non-interventional studies contributed to decision-making more when reporting was strongly influenced by the media, such as with human papillomavirus (HPV) vaccines (EMEA/H/A-20/1421), and when the outcome was unlikely to be picked up by case reports, such as exposure-outcome associations with a long latency period (e.g. Caustinerf arsenical and cancer (EMEA/H/A-31/1382)). Non-interventional studies using routinely collected data were mostly used in a similar way to studies using data collected for research (table 2). Studies using routinely collected data were used more often when the outcome was rare, whereas studies using data collected for research purposes contributed more when the outcome was poorly recorded in clinical records (e.g. Numeta G13%E/G16%E and hypermagnesemia - EMEA/H/A-107i/1373).

Referral outcomes

The majority (98%, 51/52) of referrals led to regulatory action, with the assessment committee recommending changes to the product information (83%, n=43) and particularly changes to the warnings, posology, undesirable effects and indication sections of the Summary of Product Characteristics (table 4). In 12 of 52 (23%) referrals suspension or withdrawal of marketing authorisation was recommended. Only for one referral into the safety of HPV vaccines was no change recommended.

For many referrals (42%, n=22) the assessment committee required further specific studies to be conducted, generally to elucidate safety, product usage and the effectiveness of risk minimisation measures. From a review of the assessment reports and the EU register of post-authorisation studies (EU PAS register) most of these were non-interventional studies using routinely collected data or data collected for research purposes (required in 19 referrals).

Discussion

In this comprehensive evaluation, we have shown that a wide range of evidence sources are used to aid decision making during EU drug regulatory referrals. The three types cited in the majority of assessments were randomised trials, spontaneous reports and non-interventional studies. Although non-interventional evidence is rarely cited in notifications leading to a referral, it is cited substantially during the detailed assessment of most issues, and in a few referrals was the primary evidence type used in decision-making. Notably, at the end of an assessment when recommendations were made for evidence gaps to be filled, further non-interventional evidence was required more often than any other type.

Each type of evidence appears to contribute to different aspects of a drug safety/efficacy referral, allowing for a well-rounded assessment of medication risks and benefits. Unsurprisingly, given their unique inferential advantages, randomised trials are relied on more than any other evidence type to provide evidence of drug efficacy. Current usage of non-interventional evidence for efficacy largely occurs where clinical trial data are limited. Increasingly, however, regulators require measures of drug effectiveness in routine clinical care, for which well-designed non-interventional studies and pragmatic clinical trials using routinely collected data could be highly informative.[15 19 20]

To assess safety issues non-interventional evidence is heavily relied on alongside randomised trials and spontaneous reports. Although less frequently cited, evidence from sources such as pre-clinical studies is occasionally relied on to provide information about mechanisms of effect or pharmacokinetics/pharmacodynamics.

Real world evidence can be generated from trials, such as from pragmatic trials conducted using routinely collected data. We did not identify any such trials in the assessment reports. This study design could, however, be of considerable utility given the potential for increased generalisability

relative to traditional trials, and the minimisation of confounding, through randomisation, relative to non-interventional studies.[24]

Strengths and Limitations

We were able to assess almost all referrals completed between 2013 and 2017, making this the most comprehensive summary of recent post-marketing drug regulatory decision making in Europe. The assessment reports are a comprehensive summary of the evidence used in decision making, meaning we were able to determine how each type of evidence contributed to the final recommendations.

We were unable to directly assess the quality and validity of individual studies included in the assessments. However, by reviewing the assessment reports, we evaluated how the evidence had been rated by the committees and how it had contributed to the overall decisions made. Occasionally studies were mentioned in assessment reports but no reference to a publication was given, or referencing was incomplete, and there was insufficient detail for readers to determine basic information such as the study design or setting. For example, for the assessment report on combined hormonal contraceptives (EMEA/H/A-31/1356) it was not clear whether some of the trials mentioned were randomised or not. More consistent and comprehensive referencing in assessment reports would increase the transparency of decision-making to the public and other stakeholders.

Judgement about how evidence was used in an assessment is to some extent subjective and is also reliant on what is recorded in each assessment report. However, close agreement was achieved between the two reviewers in this study.

Previous studies of the role of different evidence types in drug regulatory decision making have largely focused on marketing authorisation withdrawals/suspensions.[3-11 25] These studies highlight how the balance of evidence types has shifted over time, from heavy reliance on spontaneous reports to a more comprehensive reliance on varied evidence types including non-interventional

studies, randomised controlled trials and meta-analyses. Over a similar time period the overall number of non-interventional studies conducted and published also appears to be increasing, with studies of UK electronic primary care data a prime example of this trend.[26] With the increase in research opportunities provided by new database linkages this publication trend is likely to continue.

Unique strengths of non-interventional evidence

Non-interventional evidence was particularly useful for the assessment of product safety in situations where evidence from randomised controlled trials was limited such as the quantification of rare events, and the investigation of special populations (e.g. pregnant women and children). Whilst other types of evidence are also useful in some of these areas, our study highlighted occasions when non-interventional evidence is unique and vital for regulatory decision making. The risk of developmental disability and birth defects in the offspring of women taking valproate in pregnancy is a key example of this.[27] This rare outcome occurring in a group largely excluded from randomised trials could not have been characterised and quantified without large, well-powered non-interventional studies. Similarly, the detailed characterisation and quantification of adverse outcomes associated with NSAIDs and the oral contraceptive could not have been done without good quality non-interventional evidence. Where media interest led to stimulated spontaneous reporting, such as in the case of HPV vaccine and various adverse effects, unbiased evidence from non-interventional settings was vital in providing reassurance of safety, enabling continued use of the vaccine with no further action required. Randomised trials used to justify licensing of medicines are simply too small to detect even relatively common adverse reactions. The median number of patients studied on a new active substance is 1,708 for standard medicines and 438 for orphan medicines in the European Union[28]. Rare adverse reactions (such as those occurring in 1 in 500 patients) will not have been detected as caused by the medicine, but such rare effects can dramatically alter the benefit/risk balance of the medicine.

Where the EMA's committees call for further studies to be done, they frequently require non-interventional evidence. There is increasingly a recognition that regulatory action to minimise risks needs to be followed up to determine how effective it has been.[29] Almost all drug regulatory action involves making changes to how medicines are used in routine clinical care, and to determine whether new directives are being followed requires evidence obtained in the routine clinical care setting. Patterns of drug usage and quantification or characterisation of adverse events following regulatory action are often required; non-interventional studies will be important here, and though spontaneous reports may also be useful, they are mostly unable to give quantitative information.

There are three key elements required to ensure a successful future for non-interventional evidence within the framework of drug regulatory science. First, there are legitimate concerns regarding the use of evidence from non-interventional studies in drug regulation given the potential problems of missing data and residual confounding.[30] Through high quality study design, conduct and reporting these issues can in many cases be resolved[31]. Secondly, timely evidence is needed; non-interventional studies can be conducted rapidly in response to emerging issues, or to measure the effectiveness of past regulatory action. Thirdly, the data used in non-interventional studies needs to be of the highest standard. This includes both the quality of the data and its generalisability to the population from which it comes. Data quality can be monitored and assured by data custodians.[32] Generalisability relies on research data being drawn from a representative sample of the population. Whether data are taken from existing medical records or newly collected for a specific study, this requires the majority of patients to consent to their data to be included. For such a transaction between researchers and patients to operate successfully, maintaining anonymity and confidentiality is paramount.

Conclusions

Regulatory decision making about the safety and efficacy of medication in the European Union relies on evidence obtained from a wide range of sources; most frequently from randomised trials,

spontaneous reports and non-interventional studies. Non-interventional evidence can be vital for characterising and quantifying adverse drug reactions, is often needed for monitoring the effectiveness of regulatory action to minimise risks, and in certain situations will be the only available evidence.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: JPB had financial support from ABPI for the submitted work; IJD has received a grant from the ABPI for the study in question, financial support from GlaxoSmithKline for work unrelated to the study in question, has consulted for GlaxoSmithKline and Gilead, and holds stock in GlaxoSmithKline; SE is an independent European Commission-appointed expert member of EMA's Pharmacovigilance Risk Assessment Committee; LS reports personal fees from GSK outside the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work. The views expressed in this article are personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Author contributions: IJD conceived the study. All authors (JPB, KW, SE, KB, LS, IJD) were involved substantially in the design and planning of the study. JPB and IJD undertook the data collection and wrote the initial draft of the manuscript. JPB conducted the data analyses. All authors interpreted the results, contributed to later drafts of the manuscript, and approved the final manuscript.

Data sharing: All data analysed is available publically on the European Medicines Agency (https://www.ema.europa.eu/) and EU Register of Post-Authorisation Studies (http://www.encepp.eu/) websites.

1 **Patient consent:** Not required.

2 **Ethics approval:** Not required.

Tables

Table 1: Evidence leading to referral and evidence cited in assessment report for the 52 included referrals

	Evidence leading to referral[a]		In assessment report	
Type of evidence	**Number of referrals**	**% of all referrals**	**Number of referrals**	**% of all referrals**
Pre-clinical evidence	4	8%	29	56%
Non - randomised trials	1	2%	33	63%
Randomised trials	22	42%	48	92%
Non-interventional studies	13	25%	41	79%
i. Using routinely collected data	8	15%	31	60%
ii. Using data collected for research	6	12%	33	63%
Spontaneous reports	26	50%	38	73%
Systematic review of randomised trials	7	13%	27	52%
Systematic review of non-interventional studies	1	2%	4	8%
Systematic review combining randomised trials & non-interventional studies	0	0%	8	15%
Unclear	11	21%	33	63%

a. This was primarily based on the referral notification. However, for 12 of 52 referrals no notification was available and evidence leading to initiation was instead obtained from the assessment report and from the description of the referral on the EMA website.

Table 2: Number and percentage of all referrals (n=52) that use each type of evidence for each purpose

Type of evidence	Usage[a]						
	Mechanism	PK/PD[b]	Efficacy	Risk - Overall	Risk - subgroup	Usage of product	Effectiveness of risk minimisation measures
Pre-clinical evidence	16 (31%)	6 (12%)	2 (4%)	10 (19%)	1 (2%)	0 (0%)	0 (0%)
Non - randomised trials	1 (2%)	10 (19%)	18 (35%)	14 (27%)	2 (4%)	0 (0%)	0 (0%)
Randomised trials	3 (6%)	9 (17%)	40 (77%)	36 (69%)	7 (13%)	0 (0%)	1 (2%)
Non-interventional	3 (6%)	4 (8%)	18 (35%)	31 (60%)	5 (10%)	14 (27%)	0 (0%)
Non-interventional using routinely collected data	0 (0%)	1 (2%)	8 (15%)	25 (48%)	4 (8%)	10 (19%)	0 (0%)
Non-interventional using data collected for research	2 (4%)	4 (8%)	13 (25%)	20 (38%)	3 (6%)	7 (13%)	0 (0%)
Spontaneous reports	2 (4%)	0 (0%)	3 (6%)	37 (71%)	6 (12%)	4 (8%)	0 (0%)
Systematic review of randomised trials	0 (0%)	0 (0%)	19 (37%)	10 (19%)	1 (2%)	0 (0%)	0 (0%)
Systematic review of non-interventional studies	0 (0%)	0 (0%)	0 (0%)	4 (8%)	1 (2%)	0 (0%)	0 (0%)
Systematic review of randomised trials & non-interventional studies	0 (0%)	1 (2%)	2 (4%)	4 (8%)	0 (0%)	0 (0%)	0 (0%)
Unclear study design	1 (2%)	8 (15%)	12 (23%)	10 (19%)	0 (0%)	1 (2%)	0 (0%)

Legend

Percentage of referrals that use evidence type for each purpose	Colour
<10%	
10-19%	
20-29%	
30-39%	
40%+	

a. Usage was categorised, as detailed in the table, into: mechanism of adverse event with product usage, pharmacokinetics/pharmacodynamics of product, efficacy of product, risk of adverse events with product, risk of adverse events with product in a subpopulation, usage/misuse of a product, and effectiveness of regulatory risk minimisation measures.
b. Pharmacokinetics/pharmacodynamics

Table 3: Usage of non-interventional studies in referral assessment reports

Usage of non-interventional studies	All referrals (n=52)		Referrals leading to MA[a] withdrawal/suspension (n=12)		Referrals leading to changes to product information (n=43)	
	Number of referrals	% of all referrals	Number of referrals	% of all referrals	Number of referrals	% of all referrals
No evidence from non-interventional studies was cited in the report	11	21%	4	33%	7	16%
Evidence from non-interventional studies was cited, but made little to no contribution to the decision	11	21%	4	33%	9	21%
The decision was consistent with evidence from non-interventional studies, and also consistent with other evidence	27	52%	4	33%	24	56%
The decision was consistent with evidence from non-interventional studies AND this evidence was the primary or only factor involved in the decision e.g. there was some spontaneous reports and some large non-interventional studies	3	6%	0	0%	3	7%

a. Marketing authorisation

Table 4: Recommendations made as a result of assessment for the 52 included referrals

Recommendation	Number of referrals	% of all referrals
No change	1	2%
Further evidence before decision-making	2	4%
Suspension or withdrawal of marketing authorisation	12	23%
Change to availability	0	0%
Change to product information	43	83%
By section of the Summary of Product Characteristics:		
- Indication	24	46%
- Posology	28	54%
- Contraindications	22	42%
- Warnings	39	75%
- Interactions	14	27%
- Pregnancy	10	19%
- Driving/machinery	2	4%
- Undesirable effects	26	50%
- Overdose	3	6%
- Studies	13	25%
- Nature and contents	3	6%

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Supplementary Table 1: European Medicines Agency referrals categorised by type of referral procedure and date

Referral category	Frequency by CHMP/CMDh[a] opinion date					Total
	2013	2014	2015	2016	2017 Jan-Jun	
Article 107i procedures	5	1	0	0	0	6
Article 20 procedures	2	3	1	4	1	11
Article 31 referrals	13	13	5	3	1	35
Total	20	17	6	7	2	52

a) Committee for Medicinal Products for Human Use/Coordination Group for Mutual Recognition and Decentralised Procedures – Human

Supplementary Table 2: ATC[a] therapeutic subgroup of medicinal product by frequency for the 52 included referrals

ATC subgroup code	Subgroup definition	No. of referrals
G03	Sex hormones and modulators of the genital system	6
N02	Analgesics	6
A10	Drugs used in diabetes	3
C01	Cardiac therapy	3
M01	Anti-inflammatory and antirheumatic products	3
None	Not applicable/available	3
R05	Cough and cold preparations	3
A03	Drugs for functional gastrointestinal disorders	2
B05	Blood substitutes and perfusion solutions	2
C04	Peripheral vasodilators	2
C10	Lipid modifying agents	2
G02	Other gynelogicals	2
L01	Antineoplastic agents	2
M03	Muscle relaxants	2
N05	Psycholeptics	2
R03	Drugs for obstructive airway diseases	2
B01	Antithrombotic agents	1
B02	Antihemorrhagics	1
B03	Antianemic preparations	1
C08	Calcium channel blockers	1
C09	Agents acting on the renin-angiotensin system	1
J01	Antibacterials for systemic use	1
J02	Antimycotics for systemic use	1
J05	Antivirals for systemic use	1
L04	Immunosuppresants	1
M05	Drugs for treatment of bone diseases	1
N03	Antiepileptics	1
N07	Psychoanaleptics	1
R02	Throat preparations	1
R07	Other respiratory system products	1

a) Anatomical Therapeutic Chemical (ATC) Classification System

Supplementary Table 3: ATC[a] section of medicinal product by frequency for the 52 included referrals

ATC section	Section definition	Number of referrals
N	Nervous system	13
C	Cardiovascular system	9
A	Alimentary tract and metabolism	8
G	Genitourinary system and sex hormones	8
R	Respiratory system	7
M	Musculoskeletal system	6
B	Blood and blood forming organs	5
J	Anti-infectives for systemic use	3
L	Antineoplastic and immunomodulating agents	3
D	Dermatologicals	0
H	Systemic hormonal preparations, excluding sex hormones and insulins	0
P	Antiparasitic products, insecticides and repellents	0
S	Sensory organs	0
V	Various	0

a) Anatomical Therapeutic Chemical (ATC) Classification System

Supplementary Table 4: MedDRA[a] system organ class (SOC) of adverse event by frequency for the 52 included referrals

System Organ Class (SOC)	Number of referrals
Cardiac disorders	16
Vascular disorders	15
Nervous system disorders	9
Respiratory, thoracic and mediastinal disorders	7
Skin and subcutaneous tissue disorders	7
Gastrointestinal disorders	6
Immune system disorders	5
Infections and infestations	5
Renal and urinary disorders	5
Blood and lymphatic system disorders	4
Hepatobiliary disorders	4
Metabolism and nutrition disorders	4
Neoplasms benign, malignant and unspecified	4
Congenital, familial and genetic disorders	2
Endocrine disorders	2
Musculoskeletal and connective tissue disorders	2
Injury, poisoning and procedural complications	1
Reproductive system and breast disorders	1
Sexual function and fertility disorders	1
Surgical and Medical Procedures	1

a) Medical Dictionary for Regulatory Activities

European Medicines Agency referrals included in the study

EMA[a] Reference No.	CHMP[b] opinion/CMDh[c] position date	Referral Title
EMEA/H/C/889/A20/37 EMEA/H/C/903/A20/38 EMEA/H/C/897/A20/38	17/01/2013	Tredaptive, Pelzont and Trevaclyn
EMEA/H/A-31/1306	21/03/2013	Cilostazol-containing medicines
EMEA/H/A107i/1352	24/04/2013	Tetrazepam-containing medicines
EMEA/H/A-107i/1357	29/05/2013	Cyproterone and ethinylestradiol containing medicinal products
EMEA/H/A-31/1346	29/05/2013	Almitrine-containing medicines
EMEA/H/A-107i/1363	26/06/2013	Flupirtine-containing medicines
EMEA/H/A-31/1342	26/06/2013	Codeine-containing medicines
EMEA/H/A-31/1344	26/06/2013	Diclofenac-containing medicines
EMEA/H/A-31/1325	27/06/2013	Ergot derivatives
EMEA/H/A-31/1322	27/06/2013	Intravenous iron-containing medicinal products
EMEA/H/A-31/1314	25/07/2013	Ketoconazole-containing medicines
EMEA/H/A-107i/1373	18/09/2013	Numeta G13E and Numeta G16E emulsion for infusion
EMEA/H/A-107i/1376	23/10/2013	Hydroxyethyl starch solutions for infusion
EMEA/H/A-31/1348	23/10/2013	Hydroxyethyl starch solutions for infusion
EMEA/H/A-31/1347	23/10/2013	Short-acting beta-agonists
EMEA/H/A-31/1339	24/10/2013	Intravenous nicardipine medicines
EMEA/H/A-31/1321	24/10/2013	Metoclopramide-containing medicines
EMA/H/A-31/1361	21/11/2013	Thiocolchicoside-containing medicines
EMEA/H/A-31/1366	18/12/2013	Substances related to nicotinic acid
EMEA/H/C/275/A20/150 EMEA/H/C/276/A20/143	19/12/2013	Kogenate Bayer and Helixate NexGen
EMEA/H/A-31/1356	16/01/2014	Combined hormonal contraceptives
EMEA/H/A20/1371/C/00560-561/0039-0034	20/02/2014	Protelos and Osseor
EMEA/H/A-31/1335	20/02/2014	Methysergide-containing medicines
EMEA/H/A-31/1349	19/03/2014	Diacerein-containing medicines for oral administration
EMEA/H/A-31/1365	24/04/2014	Domperidone-containing medicines
EMEA/H/A-31/1377	24/04/2014	Zolpidem-containing medicines
EMEA/H/A-31/1382	25/04/2014	Caustinerf arsenical and Yranicid arsenical
EMEA/H/A-31/1336	25/04/2014	Linoladiol N and Linoladiol HN
EMEA/H/A-31/1370	22/05/2014	Renin-angiotensin-system (RAS)-acting agents
EMEA/H/A-107i/1395	23/07/2014	Methadone medicinal products for oral use containing povidone
EMEA/H/A-31/1391	24/07/2014	Emergency contraceptives
EMEA/H/A-31/1379	20/08/2014	Bromocriptine-containing medicines indicated in the prevention or suppression of physiological lactation post-partum
EMEA/H/C/2695/A20/0003	23/10/2014	Iclusig
EMEA/H/A-31/1383	23/10/2014	Polymyxin-containing medicines
EMEA/H/A-31/1396	19/11/2014	Testosterone-containing medicines
EMEA/H/A-31/1387	19/11/2014	Valproate and related substances
EMEA/H/A20/1404/C/000598/0031 EMEA/H/A20/1404/C/000597/0032	20/11/2014	Corlentor and Procoralan
EMEA/H/A-31/1400	25/03/2015	Hydroxyzine-containing medicinal products
EMEA/H/A-31/1394	22/04/2015	Codeine-containing medicinal products for the treatment of cough or cold in paediatric patients
EMEA/H/A-31/1401	20/05/2015	Ibuprofen- and dexibuprofen-containing medicines
EMEA/H/A-31/1398	25/06/2015	Adrenaline auto-injectors

EMEA/H/A-31/1397	18/11/2015	Ambroxol and bromhexine-containing medicines
EMEA/H/A-20/1421	19/11/2015	Human papillomavirus vaccines
EMEA/H/A-20/1419	25/02/2016	SGLT2 (sodium-glucose co-transporter 2) inhibitors
EMEA/H/A-20/1416/C/000603/0083	25/02/2016	Tysabri
EMEA/H/A-31/1420	31/03/2016	Fusafungine containing medicinal products for oromucosal and nasal use
EMEA/H/A-31/1415	28/04/2016	Inhaled corticosteroids containing medicinal products indicated in the treatment of chronic obstructive pulmonary disease
EMEA/H/A-20/1439/C/3843/0023	21/07/2016	Zydelig
EMEA/H/A-31/1432	13/10/2016	Metformin and metformin-containing medicines
EMEA/H/A-20/1438	15/12/2016	Direct-acting antivirals indicated for treatment of hepatitis C (interferon-free)
EMEA/H/A-31/1435	26/01/2017	Dienogest/ethinylestradiol-containing medicinal products indicated in acne
EMEA/H/A-20/1442	23/02/2017	SGLT2 (sodium-glucose co-transporter 2) inhibitors (previously canagliflozin)

a) European Medicines Agency
b) Committee for Medicinal Products for Human Use
c) Coordination Group for Mutual Recognition and Decentralised Procedures – Human

Definition of key terms in study

Study type	Definition
Pre-clinical evidence	Evidence from in-vitro and in-vivo (non-human animals) experimentation.
Non-randomised trials	Interventional studies where assignment to therapy was not at random or where there was only one trial arm (e.g. Phase 1 and Phase 2 trials).
Randomised trials	Interventional studies where assignment to therapy versus control was random (including both traditional multi-arm randomised controlled trials and randomised crossover trials).
Interventional studies	Clinical studies where the study investigators intervene on patient therapy.
Non-interventional studies	Clinical studies where there is no intervention by study investigators. Alternatively termed observational studies.
Spontaneous reports	Unsolicited reports of adverse outcomes reported by consumers or healthcare professionals.

Primary Data collection form

1. Basic information about referral	EMA[a] reference number	
	Initiated by (e.g. MHRA[b], European Commission)	
	Referral/procedure type	(Article 107i/Article 31/Article 20)
	Decision making model (e.g. PRAC-CMDh-EC[c])	
	Cause of referral	(Safety/Efficacy/Safety and efficacy)
	Cause of referral – description	
	CHMP[d] opinion/CMDh[e] position date	
2. Information about product and adverse event	Review title	
	Substance name	
	Product usage	
	ATC[f] group (e.g. N03 - Antiepileptics)	
	Product class (as listed on EMA website)	
	Adverse events	
	MedDRA[g] system organ classes of adverse events	
3. Determine the types of evidence leading to the referral	Source of evidence	(Notification/Assessment report/EMA webpage)
	a. Pre-clinical evidence	(Yes/No/Unclear)
	b. Non-randomised trials	(Yes/No/Unclear)
	c. Randomised trials	(Yes/No/Unclear)
	d. Non-interventional studies	(Yes/No/Unclear)
	i. Using routinely collected real world data e.g. electronic health records	(Yes/No/Unclear)
	ii. Using primary data collection e.g. pregnancy registry	(Yes/No/Unclear)
	e. Spontaneous reports	(Yes/No/Unclear)
	f. Systematic review of randomised trials	(Yes/No/Unclear)

	g. Systematic review of non-interventional studies	(Yes/No/Unclear)
	h. Systematic review combining randomised trials & non-interventional studies	(Yes/No/Unclear)
	i. Unclear design	(Yes/No)
4. a) Determine the types of evidence used in each assessment report	a. Pre-clinical evidence	(Yes/No/Unclear)
	b. Non-randomised trials	(Yes/No/Unclear)
	c. Randomised trials	(Yes/No/Unclear)
	d. Non-interventional studies	(Yes/No/Unclear)
	i. Using routinely collected real world data e.g. electronic health records	(Yes/No/Unclear)
	ii. Using primary data collection e.g. pregnancy registry	(Yes/No/Unclear)
	e. Spontaneous reports	(Yes/No/Unclear)
	f. Systematic review of randomised trials	(Yes/No/Unclear)
	g. Systematic review of non-interventional studies	(Yes/No/Unclear)
	h. Systematic review combining randomised trials & non-interventional studies	(Yes/No/Unclear)
	i. Unclear design	(Yes/No)
4. b) Summarise the types of evidence used in each assessment report	a. Pre-clinical evidence	
	b. Non - randomised trials	
	c. Randomised trials	
	d. Non-interventional studies	
	e. Spontaneous reports	
	f. Systematic review of randomised trials	
	g. Systematic review of non-interventional studies	
	h. Systematic review combining randomised trials & non-interventional studies	
	i. Unclear design	

5. Determine the recommendation made in the report.	a. No change – the available evidence dismisses any concern	(Yes/No)
	b. Further evidence before decision-making	(Yes/No)
	c. Change to product information e.g. restriction of use, addition of new adverse drug reaction, restriction of dose etc.	(Yes/No)
	d. Change to availability e.g. P to POM	(Yes/No)
	e. Suspension or revocation of marketing authorisation	(Yes/No)
	Summary of decision	
6. If there was a recommendation for a change to product information, which sections of the summary of product characteristics (SmPc) were affected?	4.1 Therapeutical indications	
	4.2 Posology and method of administration	
	4.3 Contraindications	
	4.4 Special warnings and precautions for use	
	4.5 Interactions with other medicinal products and other forms of interaction	
	4.6 Fertility, pregnancy and lactation	
	4.7 Effects on ability to drive and use machines	
	4.8 Undesirable effects	
	4.9 Overdose	
	Other	
7. Determine how non-interventional studies contributed to the decision made. Judgement is involved in this step and the assessment will be conducted independently by two researchers.	(a. No evidence from non-interventional studies was cited in the report/ b. Evidence from non-interventional studies was cited, but made little to no contribution to the decision/ c. Evidence from non-interventional studies was cited, but the decision was contrary to this evidence/ d. The decision was consistent with evidence from non-interventional studies, and also consistent with other evidence/ e. The decision was consistent with evidence from non-interventional studies AND this evidence was the primary or only factor involved in the decision/ f. Unclear)	
8. What was useful (or otherwise) about the evidence from non-interventional studies?		
9. If no non-interventional	Yes/no?	(Yes/No/Unclear)

studies were available, were such studies feasible and could they have been useful?	Further information	
10. Does the action taken as a result of the referral require future research?	Yes/no?	(Yes/No/Unclear)
	Is further non-interventional evidence required?	(Yes/No/Unclear)
	Further information	
	Design of further non-interventional studies in PAS register	(using data collected for research/ using routinely collected data)

a) European Medicines Agency
b) Medicines and Healthcare Regulatory Agency
c) Pharmacovigilance Risk Assessment Committee – Coordination Group for Mutual Recognition and Decentralised Procedures (Human) - European Commission
d) Committee for Medicinal Products for Human Use
e) Coordination Group for Mutual Recognition and Decentralised Procedures – Human
f) Anatomical Therapeutic Chemical (ATC) Classification System

Secondary data collection form - Example

EMEA/H/A-107i/1395	Pre-clinical evidence	Non - randomised trials	Randomised trials	NI[a] studies	NI studies using RCD[b]	NI studies using primary data collection	Spontaneous reports	Systematic review of randomised trials	Systematic review of NI studies	Systematic review combining randomised trials & NI studies	Unclear study design
Mechanism of AE[c] with product	No	No	No	No	No	No	Yes	No	No	No	No
Pharmacokinetics/ Pharmacodynamics	Yes	Yes	No	No	No	No	No	No	No	No	Yes
Efficacy	No	No	Yes	No	No	No	No	Yes	No	No	No
Risk - Overall	Yes	No	No	No	No	No	Yes	No	No	No	Yes
Risk - Subpopulation	No	No	No	No	No	No	No	No	No	No	No
Usage of product	No	No	No	Yes	Yes	Yes	No	No	No	No	No
Effectiveness of risk minimisation	No	No	No	No	No	No	No	No	No	No	No

a. Non-interventional studies
b. Routinely collected data
c. Adverse event