Use of Real-World Data and Evidence in Drug Development of Medicinal Products Centrally Authorized in Europe in 2018–2019

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Real-world data/real-world evidence (RWD/RWE) are considered to have a great potential to complement, in some cases, replace the evidence generated through randomized controlled trials. By tradition, use of RWD/RWE in the postauthorization phase is well-known, whereas published evidence of use in the pre-authorization phase of medicines development is lacking. The primary aim of this study was to identify and quantify the role of potential use of RWD/RWE (RWE signatures) during the pre-authorization phase, as presented in the initial marketing authorization applications of new medicines centrally evaluated with a positive opinion in 2018–2019 (*n* = 111) by the European Medicines Agency (EMA). Data for the study was retrieved from the evaluation overviews of the European Public Assessment Reports (EPARs), which reflect the scientific conclusions of the assessment process and are accessible through the EMA website. RWE signatures were extracted into an *RWE Data Matrix*, including 11 categories divided over 5 stages of the drug development lifecycle. Nearly all EPARs included RWE signatures for the discovery (98.2%) and life-cycle management (100.0%). Half of them included RWE signatures for the full development phase (48.6%) and for supporting regulatory decisions at the registration (46.8%), whereas over a third (35.1%) included RWE signatures for the early development. RWE signatures were more often seen for orphan and conditionally approved medicines. Oncology, hematology, and anti-infectives stood out as therapeutic areas with most RWE signatures in their full development phase. The findings bring unprecedented insights about the vast use of RWD/RWE in drug development supporting the regulatory decision making.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Real-world data/real-world evidence (RWD/RWE) is used widely postauthorization for addressing safety and effectiveness questions. It remains uncertain in how and to what extent RWD/RWE contributes to medicines development in the pre-approval phase.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ How much RWD/RWE contributes to early discovery and development, full development, registration/market access, and life-cycle management in pre-approval phase of innovative medicines approved through centralized procedure in Europe in 2018–2019.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ It is the first systematic evaluation of RWD/RWE use in pre-authorization phase of new drug applications evaluated in Europe.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The study confirms that RWD/RWE contribute to medicines development, learning, and regulatory decisions in virtually all phases and across different therapeutic areas and product characteristics. RWD/RWE particularly supports conditional marketing authorizations and approval of orphan medicines.

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Clinical evidence collected to support the marketing authorization of a new medicine is traditionally generated from randomized controlled clinical trials (RCTs). It is recognized, however, that RCT data have limitations, including tightly controlled conditions of clinical care, highly selected populations, and, in some scenarios, small sample sizes.[1] Multiple scientific publications, guidance, or frameworks published in recent years, suggest that real-world data (RWD) and its conversion to real-world evidence (RWE) by using applicable methodology, could provide additional insights to be used in the pre-approval phase of a medicine by mitigating several of the limitations of RCTs.[2–9] The debate over the terminology and methodologies used in real-world research of medicines is still evolving. The current terms used by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) refer to RWD as data relating to patient health status/delivery healthcare data collected from other sources than RCTs; and RWE to clinical evidence regarding the usage and potential benefits or risks of a medicinal product derived from applicable analyses of RWD (according to the FDA) or the evidence derived from the analysis and/or synthesis of RWD (according to the EMA).[10,11]

There is longstanding experience and understanding on how RWD/RWE can be utilized for monitoring of medicines' safety and effectiveness in the postauthorization phase, for example, when observing and analyzing safety signals or identifying further subpopulations with unique risk profiles.[12] However, use of RWD/RWE during drug development is less common and known, even though recent publications have boosted the promise of RWD/RWE use in the pre-approval phase to expedite the lengthy and costly medicines development phase.[13–15] The rapid pace of change in the scientific landscape for innovation, has resulted in an increase of complex products, which cannot align with traditional medicines development pathways.[16,17] The traditional conduct of clinical trials can be burdensome, unethical due to severity and rarity of disease, or unable to answer all important research questions for healthcare decision-makers.[9,18] All this challenges medicine developers and regulatory authorities to look beyond conventional sources of evidence for rapid evaluation throughout the lifecycle of medicines (e.g., through adaptive pathways and conditional approvals).[19] Applying a holistic approach to evidence generation, RWE may have potential to fill in the gaps of the current approach.

There is a growing interest to investigate and demonstrate the utility of RWD/RWE in medicines' development and to understand how its use can support the regulatory decision making. Sources that can facilitate understanding of use of RWD/RWE in drug development are scarce, although regulatory agencies have in the past decade started to provide more insights into regulatory assessments for medicinal products. An example of such a source is the European Public Assessment Reports (EPARs), which are required by the European Union Regulation Art 13(3) 726/2004, and which are publicly available at the website of the EMA.[20] The EPAR provides an overview of the assessment procedure for medicinal products approved in the European Union. It is issued by the EMA after the evaluation of all the scientific evidence submitted for the medicinal product.

Most research in this area is based on the information from the literature, including a systematic review conducted by Singh *et al*., to identify the extent to which RWD is being utilized at scale in drug development. They reported that none of the assessed publications were able to explain in detail nor quantify the scale of its use.[21] In 2020, Varnai *et al*. showed that RWE is used to provide evidence for first approvals, adding a new indication, extending an authorized indication, or argument the removal of a specific contraindication from a product label.[6] However, the difficulty to specify the role of RWD/RWE in medicines development and regulatory decision making remains.[22]

The primary aim of this study was to identify and quantify "the signatures of RWE use," defined as any reference to potential use of RWD/RWE, in medicines development and regulatory decision making for the initial marketing authorization applications of new medicines evaluated with a positive opinion received in 2018 and 2019 by the EMA. The secondary aim was to assess whether there are differences in the signatures of RWE use between specific regulatory and product characteristics.

METHODS

For this study, a cohort of medicinal products, except generics and biosimilars, centrally authorized in Europe from January 1, 2018, until December 31, 2019 ($n = 111$) was assembled. Exclusion criteria was determined based on the expectation that evidence on medicine's efficacy and safety have been derived through cross-referencing data, which is already assessed by the regulatory authority for the innovative product. Data for the study was retrieved from the EPAR overviews published at the official website of EMA.[20] The EPAR is a freely accessible regulatory document summarized by the EMA based on the information submitted by the applicant. It contains scientific discussions and technical summaries that reflect the regulatory evaluation of evidence provided by the marketing authorization holder, including quality, preclinical, and clinical data submitted in the registration dossier to support the marketing authorization application. EPARs consist of an overview, authorization details, product information, and assessment history and they can be updated throughout the lifecycle of approved medicines. Only the EPARs that were released at the moment of initial marketing authorization approval were considered for this study.

Signatures of RWE use

Signatures of RWE use were extracted from the EPAR overview, downloadable as a pdf-file, which provides an overview of the medicine in a "Question and Answer" format. This overview is written in a publicly friendly style with the aim to provide the information about the key evidence used in the approval assessment, for example, whether any comparisons with other therapeutic options available for a given treatment were considered during the evaluation process.[23] RWE signature was defined as any reference to potential use of RWD/RWE in the marketing authorization application, as presented in the EPAR overview. The key principle for identification was to assess whether the data/evidence presented was deriving from an RCT or from real world. The current terms used by the FDA and the EMA to determine RWD/RWE were our references.[10,11] To identify RWE signatures in EPAR overviews an *RWE Data Matrix* was developed by the authors (S.E., H.L., A.B., and H.G.). The *RWE Data Matrix* was based on the Bate *et al*. (2016) framework[24] and includes different stages of the drug development lifecycle where RWD/RWE can be used. Presentations from key opinion leaders, recent publications, and informal discussion with representatives from industry and regulators were used to further develop the matrix.[25–27] The *RWE Data Matrix* was tested by the authors (S.E., H.L., and H.G.) on five randomly selected EPAR overviews of the cohort and adjusted accordingly by introducing more specific questions to aid the review of the EPAR overview and the identification of the RWE signatures. The final *RWE Data Matrix* (**Table 1**) included in total 5 main categories, 6 subcategories, and 11 subcategory types, respectively. The signatures of RWE use were coded as: 0 = no signature of RWE use, 1 = signature of

Table 1 ***RWE Data Matrix*** **and examples of the exact wording of signatures of RWE use in EPAR overviews of centrally evaluated medicinal products in the European Union in 2018–2019 (*n* = 111), which led to coding of a finding (in *italics*)**

Main category	Subcategory	Types	Questions to explore whether information may derive from RWE	Category 1: Examples of *signatures of RWE use in* EPAR summary[a]	Category 2: Examples *of signatures of RWE use with data* in EPAR summary
1. Discovery	1. Epidemiology of disease	1.1 Burden of disease	Is the incidence and/or prevalence, or other epidemiological indicator of disease, addressed?	AML is rare and [Product C] *was designated an "orphan medicine"* (a medicine used in rare diseases).	[Product E] is a medicine for treating certain cancers when their cells have a mutation (change in their genes) called BRAF V600. *Up to 50% of patients with metastatic melanoma have a mutation in BRAF with forms of the V600 mutation being the most common.*
		1.2 Disease features	Are disease features (e.g., severity, symptoms, worsening, prognosis) addressed?	[Product C] *is used when AML has either come back or has not improved following previous treatment* and is only given to patients whose cancer cells have a particular change (mutation) in the gene for a protein called FLT3.	N/A[b]
		1.3 Population identification	Are there signatures for stratification of patients according to (e.g., age, gender, biomarker) nonresponse to previous treatment?	[Product F] is a vaccine used to protect *adults and children from 9 years of age* against influenza (flu).	[Product C] is used when AML has either come back or has not improved following previous treatment and *is only given to patients whose cancer cells have a particular change (mutation) in the gene for a protein called FLT3.*
2. Early development	2. Comparison to current (clinical) practice	2.1 General stratification	Is current (therapeutic) practice, alternative to the product of interest addressed?	The Agency noted that inhaled tobramycin was the "gold standard" for treatment P. aeruginosa infection in patients with cystic fibrosis and *that some patients cannot use the dry powder form because of unacceptable side effects. For these patients [Product D], which is inhaled as a solution from a nebulizer, would be a useful alternative.*	N/A[b]
3. Full development	3.1 Clinical development	3.1.1 Trial design	Is there any RWE justification of decisions for specific study design (e.g., single arm or observational), sample size, choice of comparator?	In this study, [Product A] *was not compared with any other treatment of placebo (a dummy treatment).*	In a *study of medical records of 77 patient's* treatment with [Product B] for at least 6 months, symptoms of liver disease improved in almost half (49%) of the patients treated and neurological symptoms improved in 14% of the patients.[c]
		3.1.2 Efficacy	Are there any comparative efficacy features of the product of interest, relative to current clinical practice?	The company *provided information from the published literature on the benefits* and risks of [Product G] *in the approved uses.*	In a study of medical records of 77 patient's treatment with [Product B] for at least 6 months, *symptoms of liver disease improved in almost half (49%) of the patients treated and neurological symptoms improved in 14% of the patients.*[c]
		3.1.3 Safety	Are there any comparative safety features of the product of interest, relative to current clinical practice?	[Product B] *has been used for over 30 years* to treat patients with Wilson's disease.	In terms of safety, *side effects with [Product F] are similar to those observed with vaccines containing three influenza strains and are mostly mild to moderate in severity.*

(Continued)

Table 1 (Continued)

Main category	Subcategory	Types	Questions to explore whether information may derive from RWE	Category 1: Examples of *signatures of RWE use in* EPAR summary[a]	Category 2: Examples *of signatures of RWE use with data* in EPAR summary
4. Registration /market access	4.1 Therapeutic benefit	4.1.1 Effectiveness	Is there any concrete justification/claim of relative therapeutic benefit compared to current clinical practice?	[Product A] *is effective at treating* ALK-positive NSCLC that has worsened *despite treatment with other ALK tyrosine kinase inhibitors*.	It takes less time to inhale *[Product D] than other tobramycin nebulizers and the time it takes is comparable to the time it takes to inhale the dry powder. [Product D] is therefore easier to use and might help patients to stick to their treatment*.
5. Lifecycle management	5.1 Safety profile	5.1.1 Pharmacovigilance	Are the anticipated/expected safety issues given the disease and/or population addressed?	*Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of [Product E] have been included in the summary of product characteristics and the package leaflet*.	Because of the effects on vision can lead to blindness, *[Product G] should only be used after careful assessment of possible alternatives, and patients' vision must be regularly tested during treatment*.
		5.1.2 Class effect	Are any safety class effects given the profile of the product at interest addressed?	The *side effects seen with* [Product E] *are similar to those seen with other medicines in the same class and are considered manageable*.	N/A[b]
	5.2 Clinical guidance	5.2.1 Active monitoring	Are there RWE directions for appropriate use (e.g., avoiding ineffective/unsafe use (PAES/ PASS), interactions, adherence, biomarkers)?	As for all medicines, *data on the use of* [Product D] *are continuously monitored. Side effects reported with* [Product D] *are carefully evaluated and any necessary action taken to protect patients*.	Treatment with [Product A] should be started and supervised by a *doctor who is experienced in using cancer medicines. Before starting treatment, doctors will use a genetic test to confirm that the patient has an FLT3 mutation*. The doctor will also *carry out regulator blood tests and check the patient's heart function before and during the treatment*.

[a] Category 1 = RWE signature, Category 2 = RWE signature with data. AML, acute myeloid leukemia; EPAR, European Public Assessment Reports; N/A, not applicable; NSCLC, non-small cell lung cancer; RWE, real-world evidence. Listing of example findings in EPAR overview including product ID (A–G), therapeutic area, international non-proprietary name, commercial name, conditional approval (Yes = Y/No = N), orphan medicine (Yes = Y/No = N). Product A = Anti-neoplastic and immunomodulating agent (NSCLC), Iorlatinib, Lorviqua, conditional approval (Y), orphan medicine (N). Product B = Alimentary tract and metabolism ((Hepatolenticular Degeneration), trientine dihydrochloride, Cufence, conditional approval (N), orphan medicines (N). Product C = Anti-neoplastic and immunomodulating agent (AML), gilteritinib, Xospata, conditional approval (N), orphan medicine (Y). Product D = Anti-infective for systemic use (cystic fibrosis), tobramycin, Vantobra, conditional approval (N), orphan medicine (N). Product E = Anti-neoplastic and immunomodulating agent (melanoma), encorafenib, Braftovi, conditional approval (N), orphan medicine (N). Product F = Anti-infectives for systemic use (influenza), influenza vaccine surface antigen inactivated prepared in cell cultures, Flucelvax Tetra, conditional approval (N), orphan medicine (N). Product G = Nervous system (spasms, epilepsies), vigabatrin, Kigabeq, conditional approval (N), orphan medicine (Y). [b]N/A = There were no signatures of RWE use found in this category for any of the products in the cohort (n = 111). [c]Example of an exact wording which in its context contributes to reporting in two different categories of the *RWE Data Matrix*.

RWE use, or 2 = signature of RWE use with data. For the latter one, the data was referred as any specific quantification in numbers or other details, rather than a generic description on the use of the RWD/RWE.

The qualitative review of EPAR overviews was constituted by two reviewers (S.E. and H.G.; **Figure 1**). Each EPAR was given an ID and reviewed in different order by the reviewers to minimize the bias of "learning by doing." Discrepancies in coding were discussed and in the case of doubt, or when consensus was not reached between two reviewers, the third reviewer (H.L.) was consulted.

Covariables

Information on product and marketing authorization characteristics for each medicine were collected from the "Download table of medicines," retrieved on the EMA website.[20] Information on medicine's name, therapeutic area per high-level ATC code,[28] active substance and approved condition/indication, the year of authorization and approval date, whether the medicine had received a conditional approval, was approved with the requirement of additional monitoring, or was classified as an orphan medicine were included as covariables.

Data analyses

Descriptive statistics were used to summarize the data and present the characteristics of the cohort. Cross tabulation was used as a method to quantitatively analyze and to detect trends of the relationship between multiple covariables and the signatures of RWE use across the different stages of the medicine development lifecycle and regulatory assessment. All analysis was performed using SPSS (version 27).

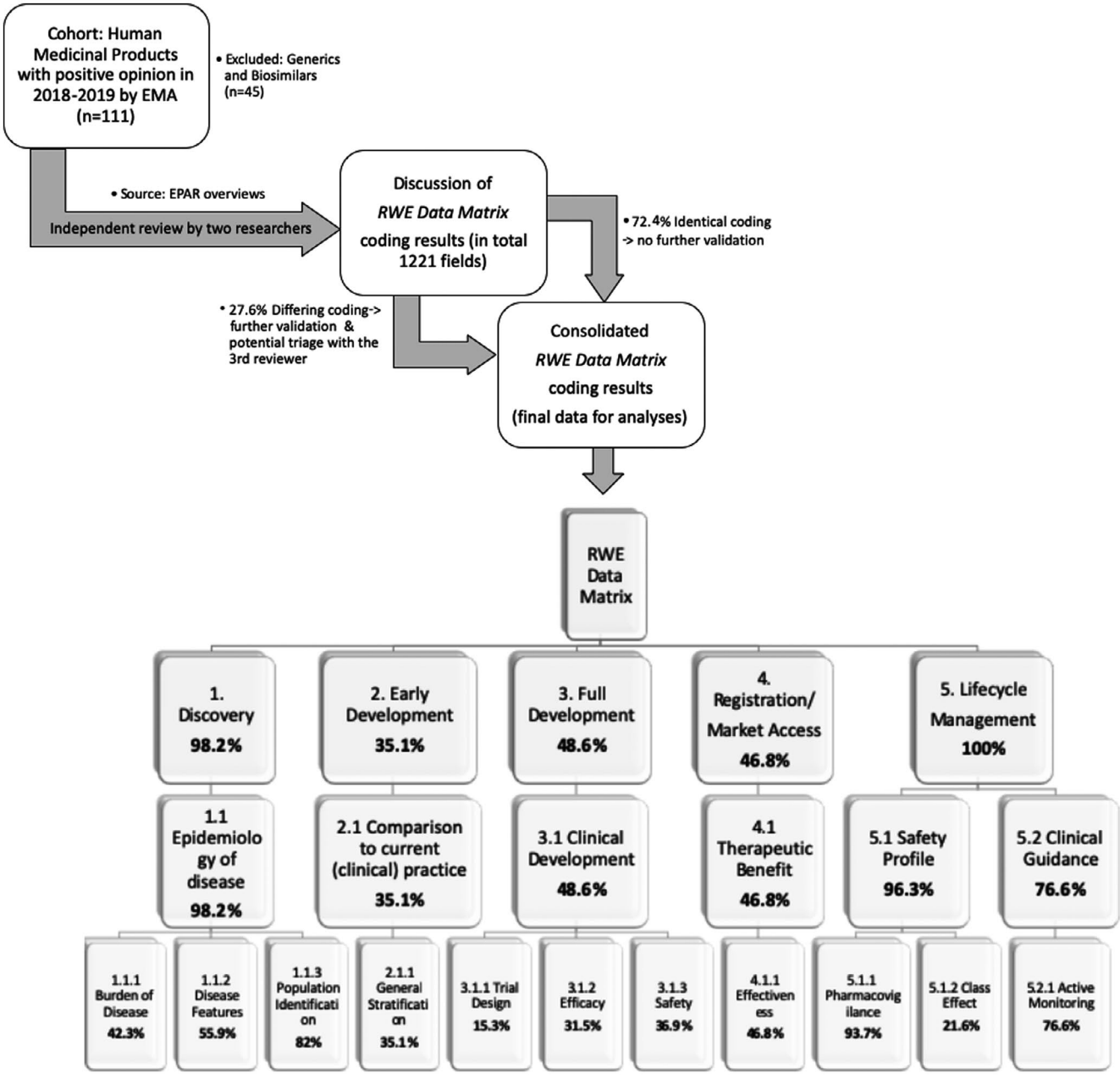

Figure 1 Review process by the *RWE Data Matrix* of EPAR overviews of centrally evaluated medicinal products by EMA in the European Union in 2018–2019 (*n* = 111) and reported RWE signatures (%) across the cohort.

RESULTS

The 111 medicinal products centrally evaluated with a positive opinion by EMA in 2018 (n = 65) and 2019 (n = 46) covered 12 different therapeutic areas, of which medicines to treat cancers (27%), infectious diseases (15.3%), nervous system disorders (14.4%), and alimentary track and metabolism disorders (12.6%) formed the most common therapeutic areas. In addition, the cohort included medicines to treat blood and blood-forming organs (9.0%), respiratory system (5.4%), musculoskeletal system (3.6%), medicines in category of "various" (3.6%), sensory organs (2.7%), cardiovascular system (1.8%), genito-urinary and sex hormones (1.8%), systemic hormonal preparations (1.8%), and one not yet classified in the Anatomic Therapeutic Chemical (ATC) system (0.9%). Additional monitoring postapproval was required for 77.5% of the products, 23.4% of products were classified as orphan medicines, whereas 8.1% were approved conditionally.

The signatures of RWE use were observed across all stages of the medicine development lifecycle (**Figure 1**, **Table 2**). Nearly all products included RWE signatures in discovery (98.2% of which 33.3% with data) and lifecycle management phase (100% of which 81.1% with data). One third of medicines had RWE signatures in early development (35.1% of which 0.9% with data), about half in full development (48.6% of which 8.1% with data) and in the registration/market access phase (46.8% of which 5.4% with data).

In the early discovery and development phase, RWD/RWE was used to identify the right patient population for the majority of the medicinal products (82.0%), whereas around half used RWD/RWE to understand the disease features (55.9%) or assessing the burden of disease (42.3%; **Figure 1**). Only a few medicinal products included information indicating use of RWD/RWE when informing trial design (15.3%) and around one third of products had RWE signatures supporting assessment of efficacy (31.5%) and safety (36.9%). Similarly, RWD/RWE was used in about a third of products (35.1%) to support comparisons to the current clinical practice in medicine's early development, whereas almost half (46.8%) used RWD/RWE to compare the therapeutic benefit and effectiveness between the new and currently available treatments. Even though all products (100%) included RWE signatures in their lifecycle management phase, and nearly all (93.7%) for pharmacovigilance, only 21.6% of products used RWD/RWE to identify class effects. Last, 76.6% of products used RWD/RWE to support their obligatory active monitoring in the postapproval phase.

The observed RWE signature patterns for the discovery and lifecycle management phase were similar when comparing approval pathways and therapeutic areas (**Table 2**). Two thirds (65.3%) of orphan medicinal products had signatures of RWE use in early development phase to support the comparison to current (clinical) practice. This was more than double when compared to non-orphans (31.8%). For orphans, the RWE signatures with data were seen for all phases of drug development and all orphans (100.0%) had RWE signatures with data in the lifecycle management phase, in comparison to 75.3% of non-orphan medicines.

The medicinal products that received a conditional marketing authorization had a different pattern of RWE signatures when compared with products that required additional monitoring or orphan medicines, and this was pronounced when looking at the use of RWE in full development and registration/market access phase. Namely, 77.8% of the conditionally approved products had RWE signatures to demonstrate their therapeutic benefit in registration/market access and 44.4% to support the trial designs when compared with orphan medicines (46.2% and 46.1%, respectively) and those that require additional monitoring (46.8% and 11.1%, respectively; **Figure 2**).

There were also some differences in the use of RWD/RWE across the therapeutic areas (**Table 2**). RWE signatures were found most in the full development phase for medicines developed as anti-infectives for systemic use (64.7%), blood and blood-forming organs (60.0%), oncology (50.0%), and alimentary track and metabolism (50.0%). In comparison, only 37.0% of medicines developed for the nervous system had signatures of RWE in this phase. Medicines for the nervous system rarely included any RWE signatures with data, whereas these were found for oncology products across all phases, being most notable in early discovery (100.0% RWE signatures of which 56.7% with data). There was a little deviation in RWE signatures in efficacy (range between 23.3% and 28.6%), whereas larger deviations were found in supporting trial design and safety (ranges between 7.1% and 23.3% and 30.0 and 53.0, respectively) across regulatory and product characteristics (**Figure 2**).

The RWE signature pattern looked very similar across the regulatory and product characteristics in the life-cycle management phase and in particular when looking at the use of RWE to support pharmacovigilance and safety aspects (**Figure 2**). The clear differences were found for class effect, ranging from 17.6% for anti-infectives to 35.7% for alimentary track and metabolism when comparing the therapeutic areas, and from 7.7% for orphans to 22.1% for additional monitoring, and 22.2% for conditionally approved products, when comparing the regulatory characteristics.

DISCUSSION

The findings of this study show that the use of RWD/RWE in the pre-approval phase is seen in virtually all phases of the drug development, but particularly in the discovery phase (i.e., epidemiology of disease and target population) and in the lifecycle phase (i.e., getting the safety profile right and for pharmacovigilance planning). We could identify relevant differences for the use of RWD/RWE in the clinical development phase stratified for clinical area or regulatory procedure (i.e., orphan, conditional approval, and additional monitoring). Signatures of RWE use including data were found for all pre-approval phases of orphan medicines. For oncology and hematology products, we observed more emphasis for the use of RWD/RWE in trial design compared with products in other clinical areas. Such differences were not seen for the use of RWD/RWE in the lifecycle phase.

Few publications have systemically assessed and quantified the publicly available regulatory evaluations and the use of RWD/RWE in them. They have rather identified single case studies, or, if done more systematically, concentrated on the applications evaluated by the FDA,[6,9,18,29] except for Baumfeld *et al*. who extracted examples from the past decade of the FDA and EMA approvals.[15] We found that all of the products in our cohort had signatures of RWE use. This finding is higher than what has been reported by Varnai,

Table 2 Signatures of RWE use of medicinal products that were subject to additional monitoring, classified as orphan medicines or received a conditional approval and the most common therapeutic areas included in the cohort of 111 medicinal products evaluated centrally by EMA in European Union in 2018–2019

	All products	Additional monitoring	Orphan medicine	Conditional approval	Anti-neoplastic and immunomodulating agents (oncology)	Anti-infectives for systemic use	Nervous system	Alimentary tract and metabolism	Blood and blood-forming organs
Number of MAAs	*n* = 111 (100.0%)	*n* = 86 (77.5%)	*n* = 26 (23.4%)	*n* = 9 (8.1%)	*n* = 30 (27.0%)	*n* = 17 (15.3%)	*n* = 16 (14.4%)	*n* = 14 (12.6%)	*n* = 10 (9.0%)
1. Discovery/epidemiology of disease									
RWE signature	98.2	98.9	96.2	88.9	100.0	94.1	100.0	92.9	100.0
RWE signature with data	33.3	32.6	42.3	55.5	56.7	23.5	12.5	28.6	30.0
2. Early development/comparison to current (clinical) practice									
RWE signature	35.1	33.7	65.3	44.4	33.3	41.2	31.3	50.0	40.0
RWE signature with data	0.9	0.0	3.8	0.0	0.0	0.0	0.0	7.1	0.0
3. Full development/clinical development									
RWE signature	48.6	43.0	50.0	55.6	50.0	64.7	37.0	50.0	60.0
RWE signature with data	8.1	7.0	11.5	0.0	13.3	11.8	0.0	7.1	10.0
4. Registration/market access/therapeutic benefit									
RWE signature	46.8	48.8	46.2	77.8	56.7	64.7	25.0	28.6	50.0
RWE signature with data	5.4	5.8	7.7	0.0	6.7	5.9	0.0	0.0	20.0
5. Lifecycle management/safety profile/clinical guidance									
RWE signature	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
RWE signature with data	81.1	81.4	100.0	88.9	96.7	64.7	75.0	78.6	80.0

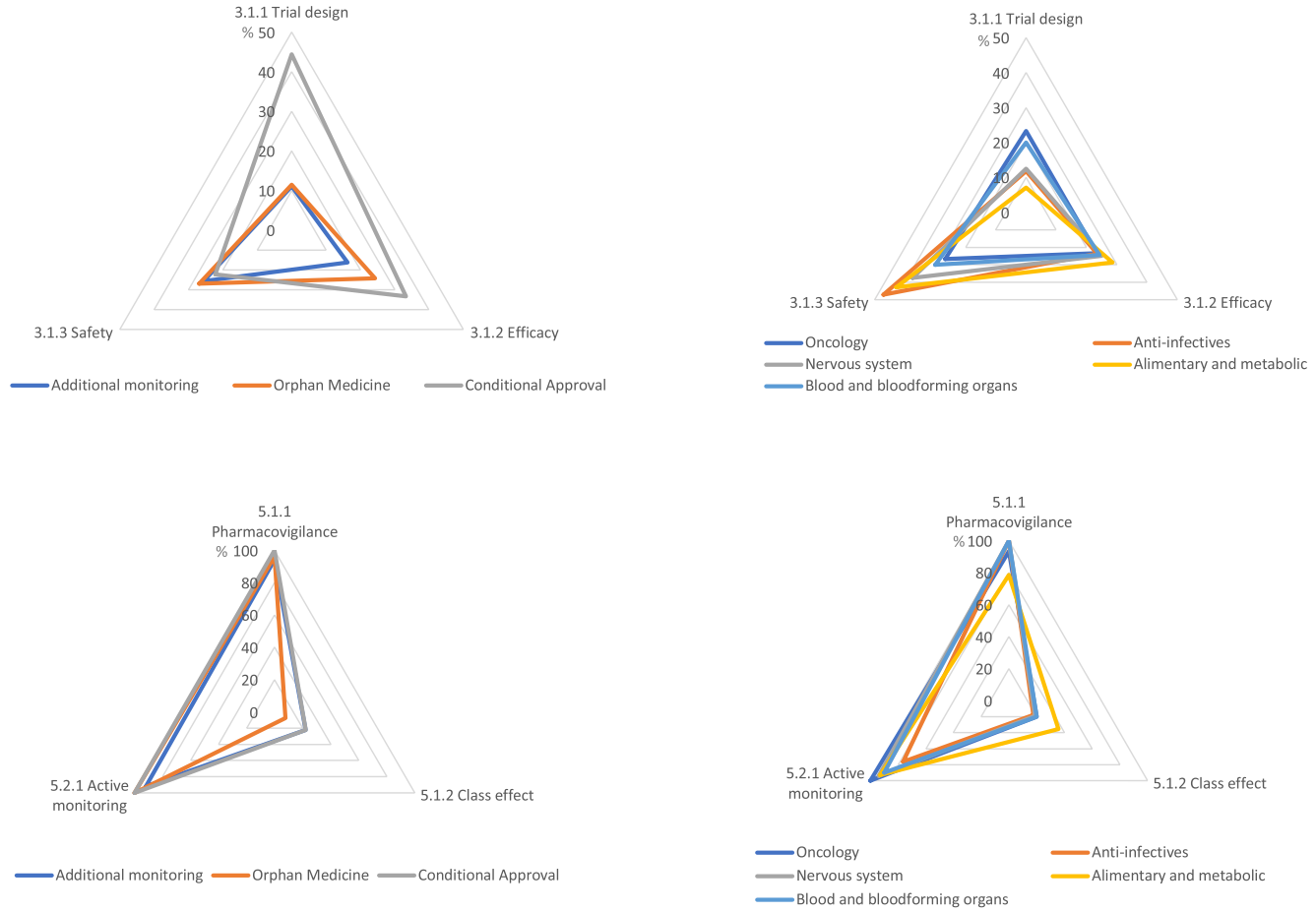

Figure 2 Patterns of RWE signatures (%) found to support the medicines development in the Full development (including trial design, safety and efficacy) and lifecycle management (including pharmacovigilance, class effect and active monitoring) for medicines that received conditional approval, were orphan medicines or required additional monitoring postapproval, and for medicines in five most common therapeutic areas of the cohort (n = 111). [Colour figure can be viewed at wileyonlinelibrary.com]

Mahendraratnam, and Aetion[6,22,30] and could be explained by the fact that our study included early discovery and lifecycle management phases as part of the evaluation, in which the RWD/RWE use is expected to be high. If these two categories were omitted, our findings would be in line with what has been reported by the others. The Aetion study concluded that 49% of the FDA-approved New Drug Applications and Biological Approvals in 2019 included an RWE study to support the efficacy/safety/effectiveness assessment, and, in 2020, this was increased to 75%. Our results concluded that 48.6% RWE signatures were found in the full development phase (safety/efficacy) and 46.8% in registration/market access phase (effectiveness) of the initial marketing authorizations.

In our study, more than half of medicines developed for cancer, anti-infectives, and hematological products had RWE signatures in the full development phase and furthermore to demonstrate effectiveness or support trial design. This is in line with findings from Mahendraratnam *et al*. who analyzed 34 publicly available examples where RWD/RWE was submitted to support effectiveness decision for products approved by the FDA between 1954 and 2020.[22] They found that 61% of these examples included RWD/RWE and the most common therapeutic areas where RWE had contributed were oncology and hematology. The use of RWD/RWE have become increasingly common and relevant, especially in oncology, because there is a growing recognition that RCTs might not be sufficiently representative of the entire patient population that is affected by cancer, and that specific clinical research questions might be best addressed by RWD/RWE.[31]

For conditionally approved medicines, RWD/RWE is considered to help addressing uncertainties in the regulatory decision making, which may rise from the complex nature of the conditions and/or the scarcity of evidence available for assessment.[32–34] Departures from traditional evidence generation through RCTs are then accompanied by increased use of RWD/RWE.[35] Our study confirms this, as medicines that received a conditional marketing authorization included notably more RWE signatures to demonstrate the product's therapeutic benefit when compared with products that received a full marketing authorization.

Similarly, as expected, we observed that orphan medicinal products have most RWE signatures, and, in particular, signatures with data in early development phase to support the comparison to current (clinical) practice, often to confirm the inadequacy of treatment options available. Our finding supports prior research in the field that RWD/RWE is used particularly in medicines developed for rare diseases.[36–38] In addition, our study demonstrates, aligned with

the literature, that RWD/RWE provides vast insights into early discovery phase, providing information on burden of disease, disease features, population identification, and stratification of patients.[39] The orphans and oncology medicines had the greatest level of RWE signatures substantiated by data in this phase, for example, by specifying the biomarker used to stratify the right patients for the treatment. Furthermore, whereas the use of RWE in the postauthorization phase is well-established for pharmacovigilance and safety reasons,[12] our study confirms that prospective RWE insights are already used to support product in its development phase and RWE signatures in this phase are greatly found as part of the initial authorization, for example, by using the existing knowledge of the potential class effects for pharmacovigilance as an element for the regulatory decision making.

The fact that RWD/RWE is reported often in the initial marketing authorization applications does not necessarily indicate anything on the quality of the evidence. Moreover, evaluating RWE in the context of regulatory decision making depends not only on the evaluation of the methodologies used to generate the evidence, but also on the reliability and relevance of underlying RWD for a specific question of interest. The "RWE signatures with data" could be considered a clearer indication of the value of RWE for a regulatory decision, but it is debatable whether the signature with such details was more valuable for regulatory decision making than a "generic RWE signature."

These constructs may raise different types of considerations for and against the increased use of RWD/RWE for regulatory decision making, as well as the weight to which it contributes to the benefit-risk evaluation.[18] Our analyses did not allow for assessing these considerations nor provided in-depth information of the use cases detected. These would be subject to further analyses of more detailed documents as part of EPAR overview (e.g., full assessment report, labeling, and RMP) or published reports of the underlying clinical studies.

It is clear that detecting the use of RWD/RWE from the publicly available regulatory documents requires effort and prior knowledge of medicines development and regulatory decision making. Our methodology required skills from the evaluators on medicines development and regulatory framework to determine what RWD/RWE is in the context of the information, as it is not in many cases labeled as such in any standard format. In addition, the inconsistencies between evaluation reports for medicinal products, published by the different regulators across the globe, makes the comparison and quantification of RWD/RWE use challenging. The importance of being able to consistently and readily identify RWD/RWE in globally available regulatory documents would provide better grounds for measuring its impact and learn any lessons about cases where it is accepted, or not, for regulatory decision making.

Exploring the potential for RWE to inform regulatory decisions is mandated in the United States by the 21st Century Cures Act.[4] It requires the FDA to establish a program to evaluate the potential use of RWE to help to support the approval of a new indication and to aid tracking. The Centers for Drug/Biologics Evaluation and Research (CDER and CBER) encourage in their draft guidance the applicants to identify submissions that include RWE being used to support a regulatory decision(s) regarding safety and/or effectiveness, and a template is proposed as an example of how applicants can identify in the cover letter accompanying the submission that the evidence package contains RWD and/or RWE.[5] Similarly, the Joint Heads of Medicines Agency (HMA)/EMA Big Data Taskforce Steering Group is currently implementing 10 priority recommendations, among which "Strengthening use of real-world data in medicines development – metadata for data discoverability and study replicability" touches upon the clear need to identify regulatory-fit RWD data sources with defined metadata describing key characteristics of these sources.[40] Transparent and consistent reporting of such RWD/RWE use as part of the application and how it contributed to regulatory decision making would be a valuable aspect to consider in further developing the EPARs.

A strength of our study is that it evaluates a full sample of all authorized innovative products, rather than samples of illustrative case studies. It is not skewed by potential company approaches and is presented in a standardized way to allow comparison. All products initially approved in 2018–2019 in Europe were included in the cohort representing multiple therapeutic areas and products with different characteristics. Due to the limited level of detail, the study did not allow determining the quality behind RWE signatures and therefore cannot give an indication on how RWD/RWE is being judged by the regulators. The inclusion of only the approved applications in the scope excludes the potential information on those applications that may have consisted of RWD/RWE but were never successful in gaining the approval.

The reporting of RWE signatures in this study is likely to be an underestimation of the true use of RWD/RWE during drug development presented for assessment to the regulatory authorities. Further analyses of full EPARs would have likely revealed more, even though this might also come with limitations as EPAR represents regulatory assessment of evidence submitted, not only the data itself. The methodology for further research should be evaluated as for this study it was considered time-consuming, risking potential subjectivity despite the safeguards put in place. An interesting angle to further examine would be to assess whether similar trends in RWE signatures would be found when systematically evaluating, with the same methodology, the evaluation/review reports of approved products issued by the other major regulators like the FDA and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan. It should be also acknowledged that global coronavirus disease 2019 (COVID-19) pandemic from 2020 onward is likely to reveal the increase of RWD/RWE use. The evolving study designs with remote trials collecting data in a real-world setting and assessing comparative safety and efficacy for COVID-19 treatments have already been underlined by recent studies.[41,42]

CONCLUSION

The findings of this study bring valuable insights to the field by underlining the RWD/RWE use in medicines development and regulatory decision making in medicines pre-approval phase. To our knowledge, this is the first systematic evaluation of such use. The results show that the use of RWD/RWE in the pre-approval phase is not only about planning postauthorization safety studies or using historical controls in single-arm pre-approval studies. RWD/RWE is present in all phases of drug development and considered as part of the authorization application. Our findings support the current efforts within the EMA and FDA, and beyond, on

more systematic use of RWE studies in new drug applications.[2,4] In addition, the strive for the improved use and greater acceptance of RWD/RWE have been announced in both joint HMA-EMA Regulatory Network Strategy[40] and EU Pharmaceutical Strategy with a potential to lead into revisions of basic pharmaceutical legislation (Dir 2001/83/EC and Reg 726/2004) by removal of any legal barriers for use of RWE (alone or complimentary) for regulatory decisions on medicines' authorization.[43] Furthermore, the pharmaceutical industry may benefit from these insights as they are looking not only to improve the quality and interoperability of RWD but also calling for a framework for RWE use in regulatory decision making and best practices for shared learning.[17,44] Medicine developers should be encouraged to continue striving for the high-quality RWE strategies in pre-approval medicines' development phase aiming for the acknowledgement by the regulators in their decision making.

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S.M.E. wrote the manuscript. S.M.E., H.G.M.L., A.B., and H.G. designed the research. S.M.E. and H.G. performed the research. S.M.E., H.G.M.L., A.B., M.L.D.B., and H.G. analyzed the data.

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