



Review

Real-World Data in the Postapproval Setting as Applied by the EMA and the US FDA

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ABSTRACT

Purpose: This article provides an analysis of the various regulatory decisions available in the public domain that suggest the use of real-world data (RWD) for postmarketing surveillance activities of products that have a marketing authorization approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The study focuses on the cases in which RWD was used for postapproval commitments or requirements (and to a lesser extent label extensions, as this has been previously published) of medicinal products comprising small molecules and biologics to support efficacy claims or confirm an acceptable safety profile.

Methods: Clarivate Analytics was commissioned to collect data from cases in which RWD was used in the postapproval settings submitted to the EMA (data were found covering the last 14 years) and the FDA (data were found spanning 23 previous years). The query resulted in 165 cases in which regulatory approval was associated with RWD. The data were then categorized and expanded with supporting information gathered from public databases and company websites.

Findings: The use of RWD to support regulatory decision-making in the postmarketing surveillance setting has increased in recent years. Most postmarketing surveillance activities are legally enforced requests on the marketing authorization holder to further document the product's safety profile. Data drawn from registries tend to be the most common source in this regard.

Implications: RWD have increasingly been used in recent years, both for new product approvals and line extensions and, as shown in this study, in the postapproval setting. There is now a growing appreciation of the potential of RWD as a source in its own right to support regulatory decision-making on the benefits and risks associated with

clinical interventions. (*Clin Ther*. 2022;44:306–322.)

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Keywords: European Medicines Agency, postapproval commitments, postapproval requirements, postmarketing, RWD, RWE, US Food and Drug Administration.

INTRODUCTION

A medical product that has been granted a marketing authorization may need to undergo additional or continuous surveillance to address specific quality, efficacy, or safety concerns that have not been achieved during its regulatory evaluation and/or where certain aspects can be assessed only under true field conditions during an extended period of time. These include, for instance, supplementary efficacy studies or more frequent monitoring for (adverse) reactions that can be specific to certain subpopulations ascertainable only through actual or large-scale use. Such studies often come in the form of postmarketing surveillance (PMS) activities.

The PMS setting can comprise a wide range of activities and includes clinical trials, spontaneous reporting systems (eg, the US Food and Drug Administration [FDA] Adverse Event Reporting System database¹), and registry studies, which provide additional information on the benefits and risks of a medical product once it enters the (general) market postauthorization. They

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could be decided upon by the developer, for instance, to expand the label, or be related to regulatory processes or procedures. In the United States, PMS activities can either be required by the regulatory authority based on specific statutes or regulations (postmarketing requirements) or are activities that the sponsor has committed to and are not imposed by specific statutes or regulations (postmarketing commitments).² In the European Union, these are normally embedded in risk management plans, periodic safety update reports, postauthorization safety studies, or postauthorization effectiveness studies, among others.³

Real-world data (RWD) are defined as routinely collected data of a patient's health status or delivery of care based on sources beyond conventional randomized clinical trials (RCTs) such as electronic health records, claims, registries, patient-generated data, or other sources that generate data on health status.^{3,4} RWD have increasingly been used in regulatory decision-making in recent years⁵ and more commonly for PMS activities.⁶ According to Berger et al,⁶ there are typically 2 cases wherein RWD could be used for PMS activities: (1) to perform confirmatory studies; or (2) in safety monitoring and surveillance of products. However, it is considered that RWD sources are more routinely used or required for safety monitoring and surveillance when it comes to PMS activities, notably by the FDA.

In the present article, we collected information available from health authority websites and published writings and provide an analysis on instances when RWD to fulfill PMS activities were applied for products that have a marketing authorization approved by the European Medicines Agency (EMA) or the FDA in the period 1998 to 2020.

MATERIALS AND METHODS

Clarivate Analytics⁷ was commissioned to collect data from cases in which RWD was used in postapproval settings to fulfill postapproval requirements or obligations, or commitment, such as for further substantiating efficacy claims or collecting additional data on the products' safety profile. These cases were submitted to the EMA in the last 14 years and the FDA in the last 23 years. The different time spans reflect the periods for which data were available and retrievable.

The initial query to Clarivate Analytics was formulated as "Research products that have used, or are using, real world evidence in the post-approval

setting in the US or the EU, evidenced as a post approval commitment (requested by the regulator); for example, in demonstrating safety or efficacy." Search results were checked as they became available, and search criteria were added or deleted over several iterations to narrow down and center the results on the subject matter at hand. Examples of search criteria included but were not limited to: regulatory jurisdiction, product name, active ingredient(s), date of approval, supplement rational, description of the postapproval data (real-world evidence [RWE]) requested/used (eg, registry, health care records), and more.

Clarivate Analytics retrieved the information from their proprietary Cortellis Regulatory Intelligence database that provides access to data such as drug pipeline, deals, and patents,⁸ but there was a difference in how it was gathered for the United States and the European Union. For the US cohort, the data were readily retrievable as they were pre-digested to the desired level of detail. For the European Union, a manual verification and selection step was required as the sought data were not readily extractable with the desired granularity. All the potential EU data points (products) had to be reviewed manually and relevant information identified to render the same level of information for both regulatory jurisdictions.

The query resulted in 165 cases in which regulatory approval was associated with RWD. The data were then categorized, elaborated, and, when required, further researched with supporting information gathered from public databases (PubMed) and company websites. Notwithstanding efforts to quality assure the dataset, we recognize that there may be some oversights or missing data points; however, these should not invalidate the overall conclusions drawn.

RESULTS

RWD Applications

The Table 1 shows the list of approved products for which RWD were used in PMS studies and for which the study protocol was accepted by either the EMA or the FDA. Both international nonproprietary and brand names are provided throughout the text to facilitate comparisons across jurisdictions. A total of 165 products were identified, of which 109 are products approved by the EMA between 2007 and 2020 and 56 approved by the FDA between 1998 and 2020.

Table 1. List of products approved by the EMA and the US FDA with the use of RWD for post-marketing surveillance, by year. Both international nonproprietary and brand names (in upper case) are provided to help the reader make comparisons across jurisdictions if desired.

EMA-approved products (109)	US FDA-approved products (56)
2007	1998
1. Epoetin zeta (SILAPO)	1. Infliximab (REMICADE)
2. Eculizumab (SOLIRIS)	2003
2009	2. Pegvisomant (SOMAVERT)
3. Tocilizumab (ROACTEMRA)	2004
2012	3. Emtricitabine/ténofovir disoproxil (TRUVADA)
4. Dinutuximab beta (QARZIBA)	2009
2014	4. Etonogestrel (IMPLANON/NEXPLANON)
5. Abacavir dolutegravir lamivudine (TRIUMEQ)	2010
2015	5. Denosumab (PROLIA/XGEVA)
6. Eliglustat (CERDEGLA)	2011
7. Secukinumab (COSENTYX)	6. Deferasirox (EXJADE)
8. Atazanavir; cobicistat (EVOTAZ)	2017
9. Tolvaptan (JINARC)	7. Morphine sulfate (ARYMO ER)
10. Cangrelor (KENGREXAL)	8. Dupilumab (DUPIXENT)
11. Bupropion naltrexone (MYSIMBA)	9. Ocrelizumab (OCREVUS)
12. Apremilast (OTELZA)	10. House dust mite (ODACTRA)
13. Levofloxacin (QUINSAIR)	11. Midostaurin (RYDAPT)
14. Rasagiline (RASAGILINE RATIOPHARM)	12. Brodalumab (SILIQ)
15. Liraglutide (SAXENDA)	13. Naldemedine (SYMPROIC)
16. Omibitasvir (VIEKIRAX)	14. Hydrocodone bitartrate (VANTRELA ER)
17. Safinamide (XADAGO)	2018
2016	15. Erenumab (AIMOVIG)
18. Efтренонаког alpha (ALPROLIX)	16. Fremanezumab-vfrm (AOVY)
19. Etanercept (BENEPALE)	17. Ethinylestradiol, segestrone acetate (ANNOVERA)
20. Brivaracetam (BRIVIACT)	18. Stiripentol (DIACOMIT)
21. Emtricitabine; tenofovir alafenamide (DESCOVI)	19. Galcanezumab-gnIm (EMGALITY)
22. Elotuzumab (EMPLICITI)	20. Cannabidiol (EPIDIOLEX)
23. Tenofovir disoproxil (TENOFOVIR DISOPROXIL MYLAN)	21. Amifampridine (FIRDAPSE)
24. Sofosbuvir; velpatasvir (EPLCUSA)	22. Migalastat (GALAFOLD)
25. infliximab (FLIXABI)	23. Tildrakizumab asmn (ILUMYA)
26. Octocog alfa (KOVALTRY)	24. Tolvaptan (JINARC)
27. Tipiracil; trifluridine (LONSURF)	25. Prucalopride (MONTEGRITY)
28. Emtricitabine; rilpivirine; tenofovir alafenamide (ODEFSEY)	26. Patisiran (ONPATTRO)
29. Pandemic influenza vaccine (H5N1) (live attenuated, nasal) (PANDEMIC INFLUENZA VACCINE ASTRAZENECA)	27. Elagolix sodium (ORLISSA)
30. Glycopyrronium bromide (SIALANAR)	28. Mogamulizumab-kpkc (POTELIGEO)
	29. Inotersen (TEGSEDI)

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Table 1. (*continued*)

EMA-approved products (109)	US FDA-approved products (56)
31. Autologous CD34+ enriched cell fraction (STRIMVELIS)	2019
32. Tenofovir disoproxil (TENOFOVIR MYLAN)	30. Lemborexant (DAYVIGO)
33. Selexipag (UPTRAVI)	31. Dengue tetravalent vaccine live (DENGVAXIA)
34. Pitolisant (WAKIX)	32. Cladribine (MAVENCLAD)
2017	33. Siponimod (MAYZENT)
35. Avelumab (BAVENCIO)	34. Pretomanid (PRETOMANID)
36. Cerliponase alfa (BRINEURA)	35. Cilastatin, imipenem, relebactam (RECARBRIOS)
37. Chenodeoxycholic acid (CHENODEOXYCHOLIC ACID SIGMA-TAU)	36. Lasmiditan (REYVOW)
38. Dupilumab (DUPIXENT)	37. Amifampridine (RUZURGI)
39. Efavirenz; emtricitabine; tenofovir disoproxil (EFAVIRENZ)	38. Semaglutide (RYBELSUS)
40. Sarilumab (KEVZARA)	39. Afamelanotide (SCENESSE)
41. Lacosamide (LACOSAMIDE ACCORD)	40. Risankizumab-rzaa (SKYRIZI)
42. Lutetium 177 Lu oxodotreotide (LUTATHERA)	41. Solriamfetol (SUNOSI)
43. Cladribine (MAVENCLAD)	42. Ubrogepant (UBRELVY)
44. Parathyroid hormone (NATPAR)	43. Diroximel fumarate (VUMERITY)
45. Naloxone (NYXOID)	44. Bremelanotide (VYLEESI)
46. Baricitinib (OLUMIANT)	45. Tafamidis meglumine (VYNDAMAX)
47. Baricitinib (REFIXIA)	46. Pitolisant (WAKIX)
48. Rituximab (RIXATHON)	47. Cenobamate (XCOPRI)
49. Dimethyl fumarate (SKILARENCE)	48. Lefamulin (XENLETA)
50. Nusinersen (SPINRAZA)	2020
51. Guselkumab (TREMFYA)	49. Influenza A (H5N1) monovalent vaccine, adjuvanted (AUDENZ)
52. Meningococcal group B vaccine (TRUMENBA)	50. Bempedoic acid (NEXLETOL)
53. Tenofovir alafenamide (VEMLIDY)	51. Ezetimibe; bempedoic acid (NEXLIZET)
54. Sofosbuvir / velpatasvir / voxilaprevir (VOSEVI)	52. Rimegepant (NURTEC ODT)
55. Tofacitinib (XELJANZ)	53. Peanut (arachis hypogaea) allergen powder-dnfp (PALFORZIA)
2018	54. Levonorgestrel; ethinyl estradiol (TWIRLA)
56. Erenumab (AIMOVIG)	55. Eptinezumab-jjmr (VYEPTI)
57. Bictegravir / emtricitabine / tenofovir alafenamide (BIKTARVY)	56. Ozanimod (ZEPOSIA)
58. Buprenorphine (BUVIDAL)	
59. Doravirine / lamivudine / tenofovir disoproxil (DELSTRIGO)	
60. Dengue tetravalent vaccine (DENGVAXIA)	
61. Galcanezumab (EMGALITY)	
62. Benralizumab (FASENRA)	
63. Influenza vaccine surface antigen (FLUCELVAX TETRA)	

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Table 1. (*continued*)

EMA-approved products (109)	US FDA-approved products (56)
64. Emicizumab (HEMLIBRA)	
65. Adalimumab (HULIO)	
66. Tildrakizumab (ILUMETRI)	
67. Prasterone (INTRAROSA)	
68. Damoctocog alfa pegol (JIVI)	
69. Dolutegravir sodium; rilpivirine hydrochloride (JULUCA)	
70. Tisagenlecleucel (KYMRIAH)	
71. Velmanase alfa (LAMZEDE)	
72. Voretigene neparvovec (LUXTURNA)	
73. Vestronidase alfa (MEPSEVII)	
74. Mexiletine (NAMUSCLA)	
75. Neratinib (NERLYNX)	
76. Patisiran (ONPATTRO)	
77. Semaglutide (OZEMPIC)	
78. Doravirine (PIFELTRO)	
79. Insulin glargine (SEMGLEE)	
80. Tezacaftor / ivacaftor (SYKEVI)	
81. Inotersen (TEGSEDI)	
82. Ulipristal acetate (ULIPRISTAL)	
83. Ciclosporin (VERKAZIA)	
84. Voncog alfa (VEYVONDI)	
85. Axicabtagene ciloleucel (YESCARTA)	
2019	
86. Fremanezumab-vfrm (AJOVY)	
87. Zanamivir (DECTOVA)	
88. Dolutegravir / lamivudine (DOVATO)	
89. Cannabidiol (EPIDIOLEX)	
90. Turoctocog alfa pegol (ESPEROCT)	
91. Pegvaliase (PALYNZIQ)	
92. Netarsudil (RHOKIINSA)	
93. Upadacitinib (RINVOQ)	
94. Naldemedine (RIZMOIC)	
95. Buprenorphine (SIXMO)	
96. Risankizumab (SKYRIZI)	
97. Esketamine (SPRAVATO)	
98. Ibalizumab (TROGARZO)	
99. Ravulizumab (ULTOMIRIS)	
100. Volanesorsen (WAYLIVRA)	
101. Hydroxycarbamide (XROMI)	
102. Sotagliflozin (ZYNQUISTA)	
103. Autologous CD34+ cells encoding βA-T87Q-globin gene (ZYNTEGLO)	

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Table 1. (*continued*)

EMA-approved products (109)	US FDA-approved products (56)
2020	
104. Givosiran (GIVLAARI)	
105. Osilodrostat (ISTRURISA)	
106. Siponimod (MAYZENT)	
107. Metreleptin (MYALEPTA)	
108. Fostamatinib (TAVLESSE)	
109. Live oral cholera vaccine (VAXCHORA)	

The distribution of products according to year shows an increasing number of products being approved in recent years, notably between 2015 and 2020, with the highest number of approved products in 2018 (30 products) for the EMA and in 2019 (19 products) for the FDA.

There are 13 cases (of the 165) in which the same products were approved by both the EMA and the FDA. These include cannabidiol (Epidiolex® [Greenwich Biosciences, Carlsbad, CA, USA]), cladribine (Mavenclad® [Merck KGaA, Darmstadt, Germany]), dengue tetravalent vaccine (live) (Dengvaxia® [Sanofi Pasteur Inc, Bridgewater Township, NJ, USA]), dupilumab (Dupixent® [Sanofi Biotechnology, Paris, France]), erenumab (Aimovig® [Biohaven Pharmaceuticals, Inc, New Haven, CT, USA]), fremanezumab-vfrm (Ajovy® [Teva Pharmaceuticals USA, Inc, North Wales, PA, USA]), tegsedi (Inotersen® [Akcea Therapeutics, Inc, Boston, MA, USA]), galcanezumab (Emgality® [Eli Lilly and Company, Indianapolis, IN, USA]), patisiran (Onpattro® [Alnylam Pharmaceuticals, Inc, Cambridge, MA, USA]), pitolisant (Wakix® [Bioprojet Pharma SAS, Antwerp, Belgium]), risankizumab (Skyrizi® [AbbVie Inc, North Chicago, IL, USA]), mayzent (Siponimod® [Novartis AG, Basel, Switzerland]), and tolvaptan (Jinarc® [Otsuka America Pharmaceutical, Inc, Princeton, NJ, USA]).

Postmarketing Type and Categories

Most PMS activities suggesting the use of RWD for products approved by the FDA have been categorized as a requirement. Only in 6 of the 56 products are PMS activities considered as a commitment; that is, either proposed by the sponsor or not imposed by a regulatory statute. These include influenza A

(H5N1) monovalent vaccine (Audenz® [Seqirus Inc, Holly Springs, NC, USA]), dengue tetravalent vaccine (Dengvaxia®), etonogestrel (Nexplanon® [Organon & Co, Jersey City, NJ, USA]), house dust mite (*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*) allergen extract (Odactra™ [ALK-Abelló A/S, Hørsholm, Denmark]), infliximab (Remicade® [Janssen Biotech, Inc, Horsham, PA, USA]), and peanut (*Arachis hypogaea*) allergen powder-dnfp (Palforzia® [Aimmune Therapeutics, Brisbane, CA, USA]).

Similarly, the majority (84 of 109) of the PMS activities suggesting the use of RWD for products approved by the EMA are categorized as requirements. **Figure 1** presents the distribution of these requirements based on their category; 79% are classified as Category 3, postmarketing requirements that are legally enforced to investigate a safety concern as part of the pharmacovigilance plan of an authorized medicinal product.⁹ The remaining PMS activities are then categorized accordingly as Category 1 (12%), activities essential for the benefit-risk profile of the product, or as Category 2 (9%), specific obligations to be fulfilled in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.

Classification by Therapy Type and Specialty Area

Figure 2 shows the percent distribution of approved products with a PMS obligation or commitment by product type according to the EMA and the FDA. For both the EMA and the FDA, a large majority of products are classified as small molecules. For products approved by the EMA, 61% of these are classified as small molecules and 31% as biologics; for the

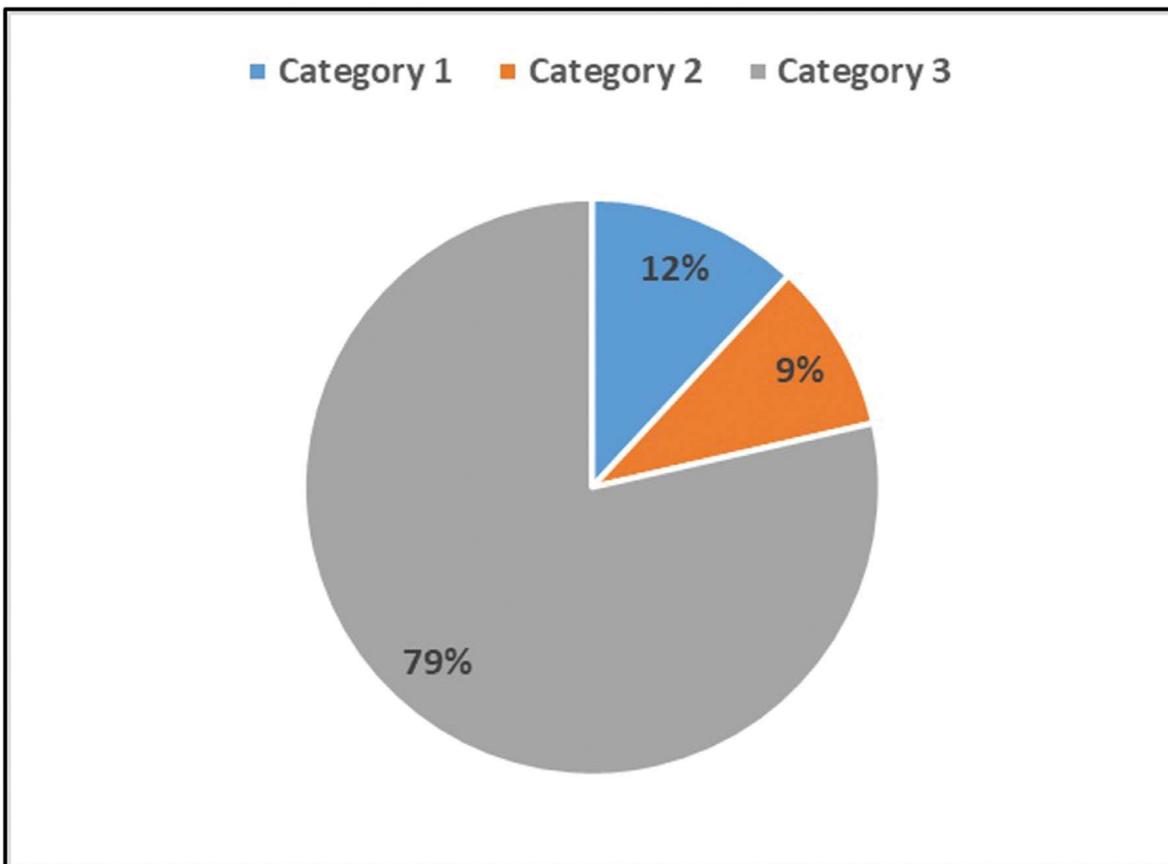


Figure 1. Postmarketing requirement categories of products approved by the European Medicines Agency. Definitions are according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (<http://www.encepp.eu/encepp/studies/help/studies1.html>). Category 1 is imposed as a condition of the marketing authorization because it is key to the benefit-risk profile of the product. Category 2 may be a specific obligation in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstance. Category 3 is a requirement to investigate a safety concern as part of the pharmacovigilance plan of an authorized medicinal product. Source: Authors' elaboration based on data from Clarivate Analytics.

FDA, 62% are classified as small molecules, 34% as biologics, and 4% as medical devices.

In terms of therapeutic area, most medical products approved by the EMA with PMS suggesting the use of RWD include treatments for infectious or parasitic diseases (23 products); endocrine, nutritional, or metabolic diseases (18 products); blood or blood-forming organ diseases (13 products); immune system diseases (12 products); and nervous system diseases (11 products) (Figure 3). However, the largest number of medical products approved by the FDA for this case includes treatments for nervous system diseases (20 products) such as insomnia, migraine

disorders, multiple sclerosis, seizures, and severe pain management (Figure 4).

Data Type and Source

Of the combined 165 products approved by both regulatory authorities, 68% suggest the use of secondary data or data that are collected through registries, medical records, or other commissioned studies.

More specifically, Figure 5 shows the breakdown of these suggested data sources for PMS for the EMA and the FDA. For the EMA, RWD are suggested or required to be sourced from registries (71 products),

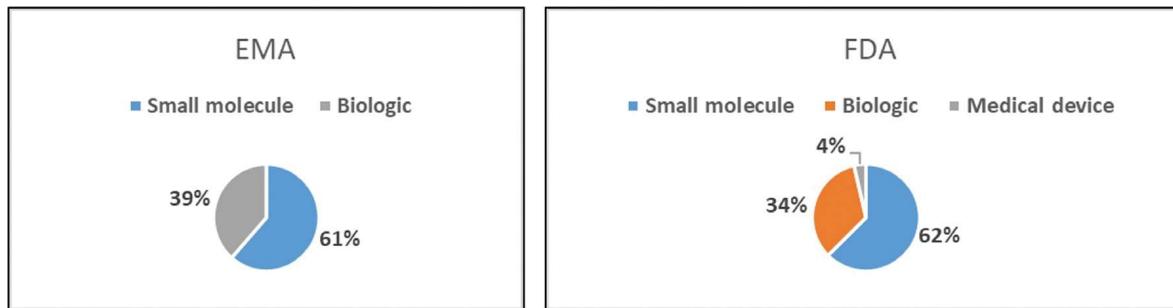


Figure 2. Percent distribution of products approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) according to product type. Source: Authors' elaboration based on data from Clarivate Analytics.

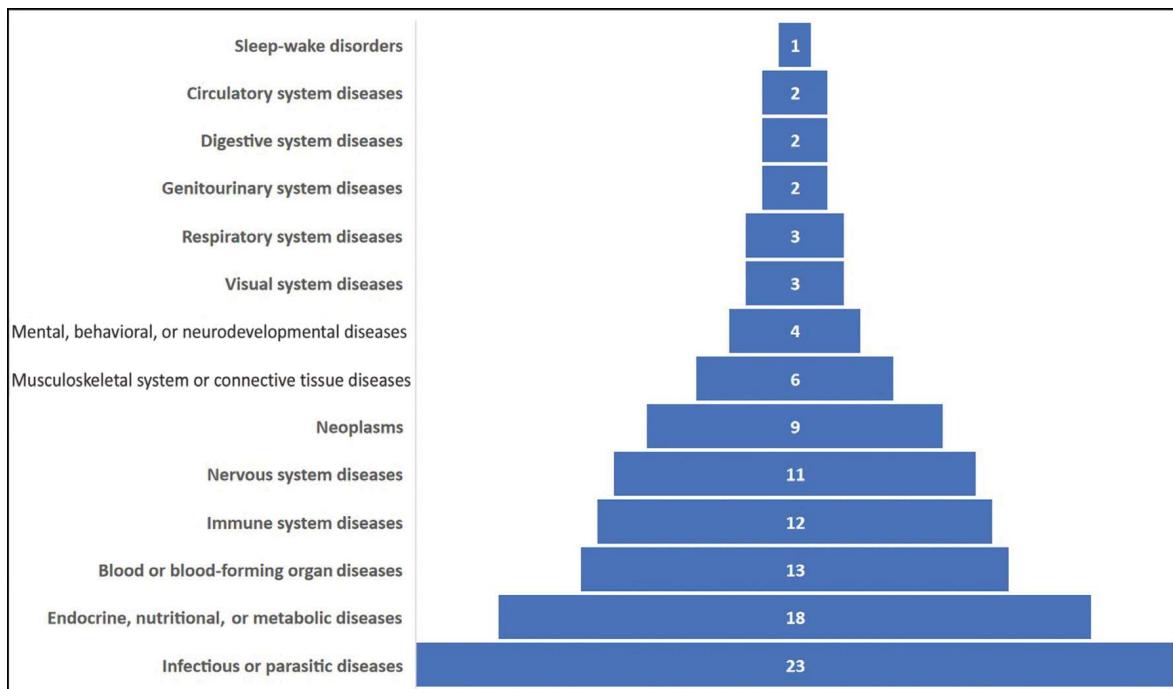


Figure 3. Number of products approved by the European Medicines Agency with a postmarketing surveillance obligation or commitment according to therapeutic area. Classification was based on World Health Organization International Classification of Diseases 11th Revision (<https://icd.who.int/>). Source: Authors' elaboration based on data from Clarivate Analytics.

observational studies (35 products), open cohort studies (2 products), and a claims database (1 product). For the FDA, these are suggested or required to be sourced from registries (34 products), observational studies (16 products), and medical records (6 products).

PMS activities that are to be sourced from registries have been further classified into 3 specific categories:

disease, patient, or product registry. For the EMA (Figure 6), 49% of these are to be sourced from patient registries, 48% from product registries, and 3% from specific disease registries. However, for the FDA, 85% of these are to be sourced from product registries, 12% from patient registries, and 3% from disease registries.

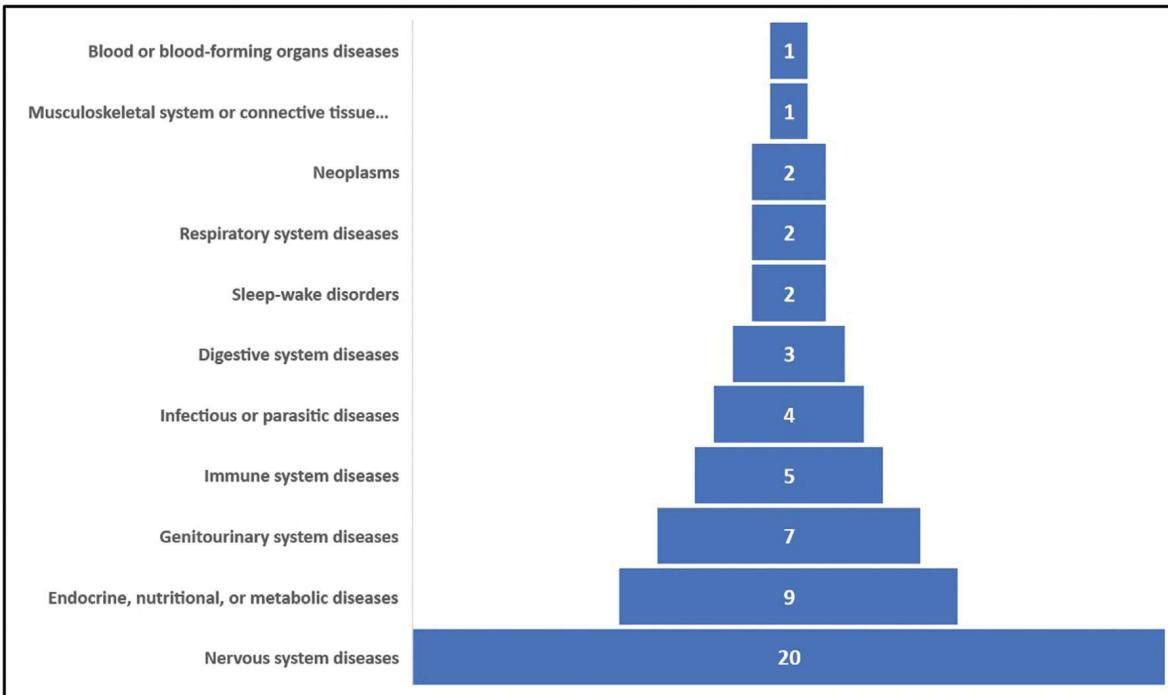


Figure 4. Number of products approved by the US Food and Drug Administration with a postmarketing surveillance obligation or commitment according to specialty area. Classification was based on World Health Organization International Classification of Diseases 11th Revision (<https://icd.who.int/>). Source: Authors' elaboration based on data from Clarivate Analytics.



Figure 5. Source of postmarketing surveillance for products approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Note the difference in scale. Source: Authors' elaboration based on data from Clarivate Analytics.

Data Use

Data from PMS activities were also classified based on the objective, such as for monitoring safety, efficacy, or effectiveness, as well as in further characterizing the product or the disease it aims to treat (eg, in its use,

effects in a specific population, or in determining a disease's outcome[s] or natural history based on the treatment). Of the 109 products approved by the EMA, RWD collected for 51 products are used to address one specific objective. As shown in Figure 7A, RWD are

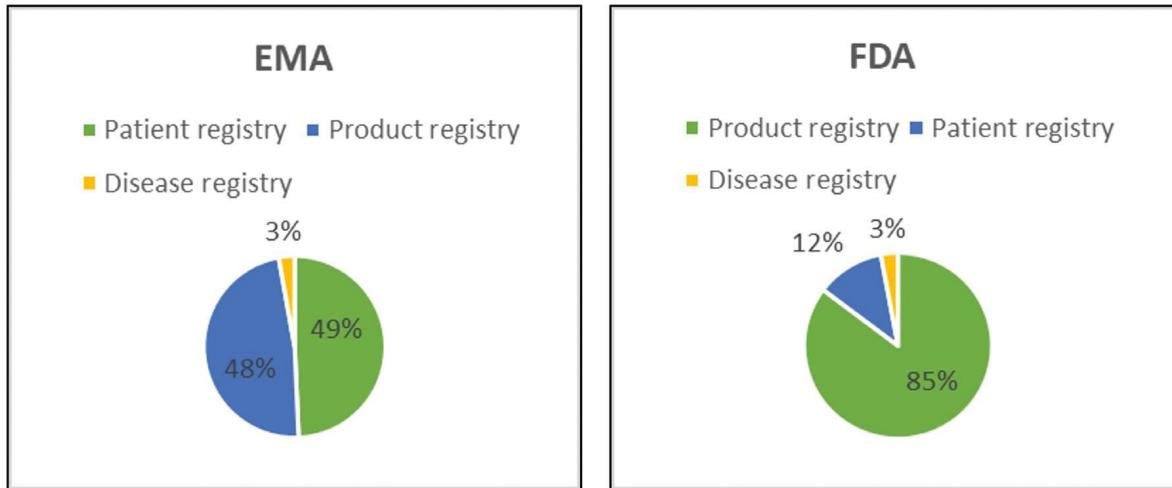


Figure 6. Type of registries for products approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Disease registries record information on a specific disease, patient registries on a specific subset of a population, and product registries record information relating to the product (eg, safety or related adverse events). Source: Authors' elaboration based on data from Clarivate Analytics.

primarily collected to address specific safety issues. For 39 cases, in which at least a combination of 2 specific objectives are met, these usually aim at addressing safety issues and in characterizing the effects of the treatment on a specific subset of a population, which is often aimed at children and/or pregnant women.

For the FDA, 14 products associated with only 1 postmarketing activity, and RWD are similarly primarily used to validate the products' safety profile (50%) (Figure 7B). Of the 56 approved products, RWD for PMS activities are expected to be used in addressing at least two (21 products) or three (20 products) specific objectives. For those meeting at least 2 objectives, ~16 products aim at providing RWD related to characterizing the disease outcomes and/or determining the natural history of the product as well as characterizing the effects on a specific subset of the population. For those meeting a combination of at least 3 characteristics, these meet the same reasons as previously mentioned with the addition of addressing specific safety issues.

Submission Timelines

Submission timelines of postapproval data for products approved by both the EMA and the FDA are mostly imposed within a long-term period or for

a period beyond 6 years. Figure 8 shows that this is the case for ~79 products approved by the EMA and for ~47 products approved by the FDA. For the EMA, these include products in which periodic safety update reports have been required, as they are part of an ongoing review and are reported whenever it is made available; hence, with an undefined timeline.

As for the rest of the products, <17% and 15% of products approved, respectively, by the EMA and the FDA have submission timelines imposed in the midterm (5–6 years). An even more limited number of products have been approved with submissions in the short-term period (<5 years).

DISCUSSION

RWD as a Postapproval Tool

Postapproval requirements are measures that sometimes are invoked by regulators in connection with the approval of a medicinal product. According to the EMA, the applicant/marketing authorization holder should provide additional data postauthorization, as necessary from a public health perspective, to complement the available data (at approval) with additional studies on the safety and, in certain cases, the efficacy or quality of an authorized medicinal product.¹⁰ A revised guideline on postapproval measures that

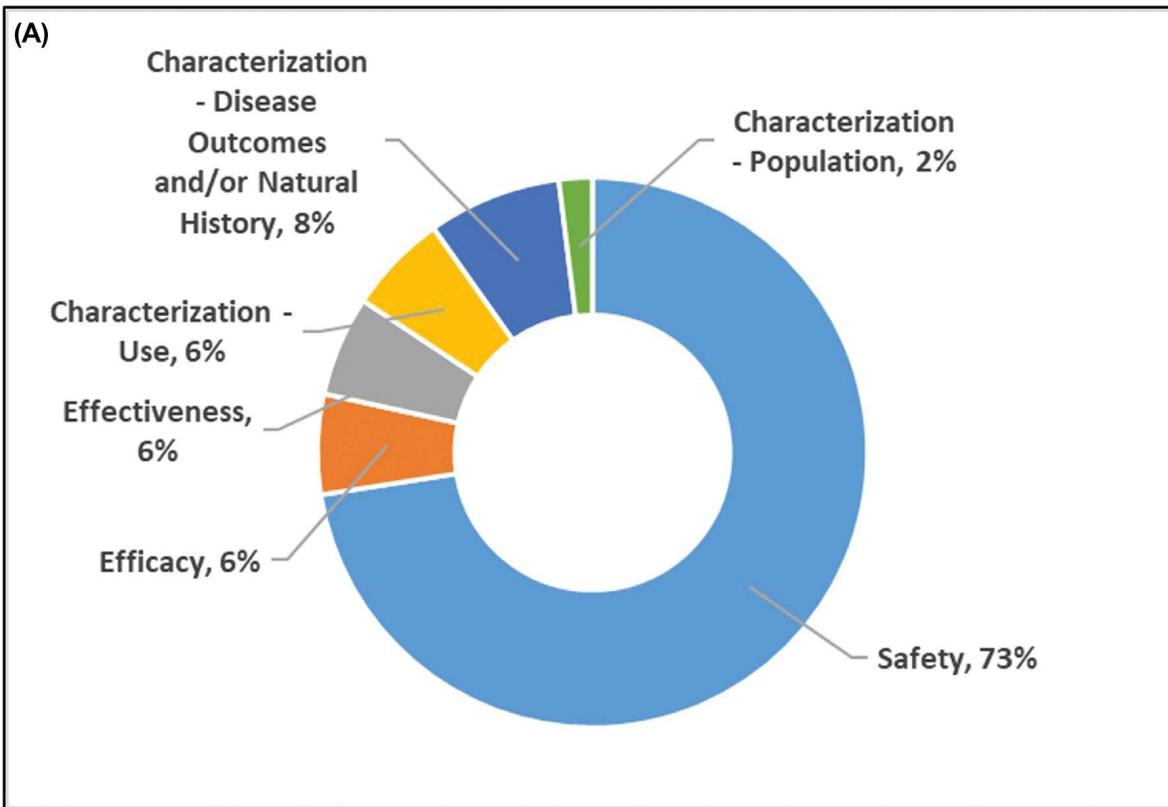


Figure 7. (A) Percent distribution on the use of real-world data in the European Union for 51 products meeting at least one specific postmarketing objective. Source: Authors' elaboration based on data from Clarivate Analytics.

illustrate the plethora of available tools was recently published and includes specific obligation, annex II condition, additional pharmacovigilance activities in the risk management plan, legally binding measure, and recommendation.¹⁰

Compared with the limited number of examples in which RWD have been used for new approvals and line extensions,⁵ the use of RWD for PMS activities is not uncommon and has been increasingly used in PMS activities for products approved by both the EMA and the FDA, notably in recent years; this is possibly because RWD readily lends itself to investigating the safety or efficacy profile of a product in a real-life setting. We do not know the reason why the number of cases trailed off toward the end of the study period (ie, toward the 2019–2020 time frame) but speculate that this could be an effect of the coronavirus disease 2019 pandemic shifting focus of the entire pharma sector.

Our data set comprises 165 entries that are subdivided into many smaller cohorts not readily lending themselves to elaborate statistical analyses comparing the 2 agencies. One tangible regulatory postapproval example in the European Union is the application of RWD in the re-evaluation of metformin, which is one of the most commonly prescribed oral antidiabetes drugs to treat early type 2 diabetes. Upon review of the available RWD, the EMA's Committee for Medicinal Products for Human Use (CHMP) supported labeling changes, including a revision of the indication and contraindications.¹¹ The FDA has also included RWD in their decision-making processes and has outlined a framework and guidance for the use of RWD/RWE as part of their Prescription Drug User Fee Act VI commitments.^{4,12}

Although the majority of products have been approved in recent years, there have been specific cases in which products have been approved in the last 2

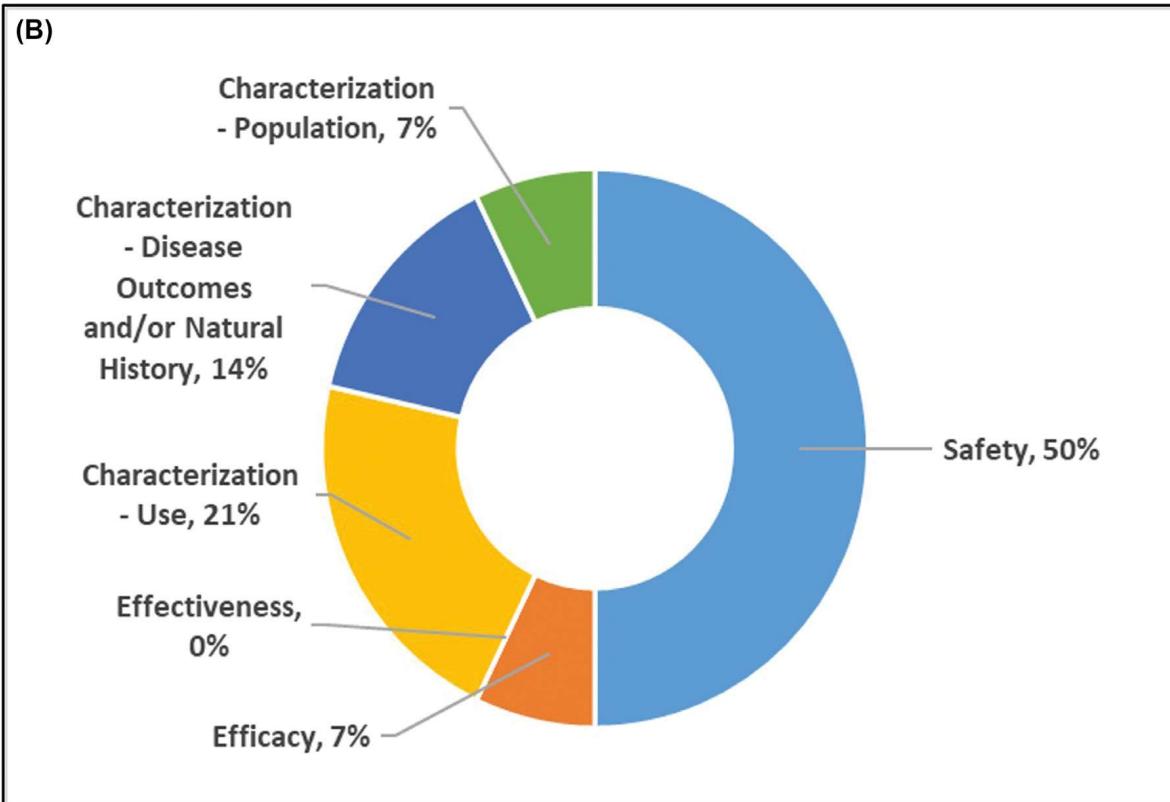


Figure 7. (B) Percent distribution on the use of real-world data in the United States for 14 products meeting one specific postmarketing objective. Source: Authors' interpretation and elaboration based on data from Clarivate Analytics.

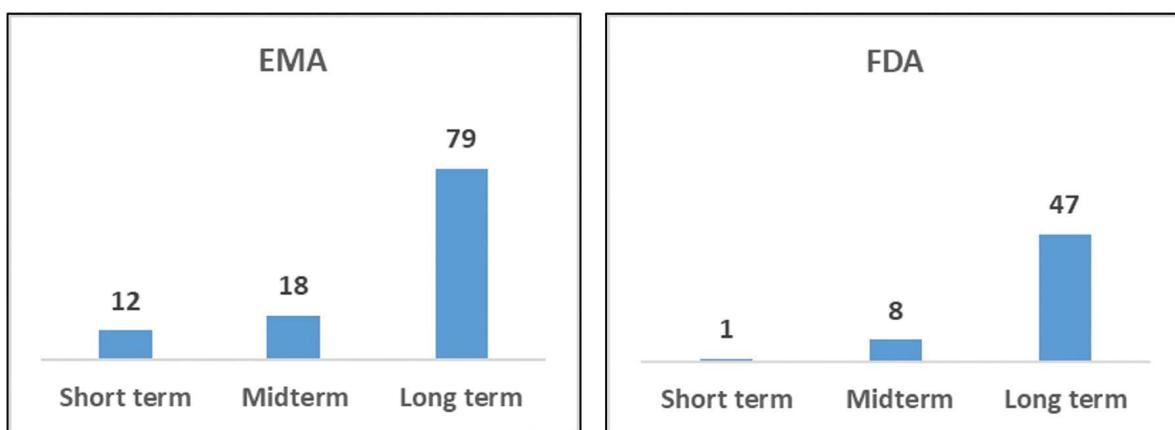


Figure 8. Submission timelines of Post Approval Commitments for products approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). Timelines are defined as short term (<5 years), midterm (5-6 years), and long term (>6 years). For the EMA, products with periodic safety update reports are categorized as long term with an undefined timeline. Source: Authors' elaboration based on data from Clarivate Analytics.

decades and have collected, or are collecting, long-term RWD to fulfill PMS activities. These include the case of epoetin zeta (Silapo® [STADA Arzneimittel AG, Bad Vilbel, Germany]),¹³ eculizumab (Soliris® [Alexion Pharmaceuticals, Inc, New Haven, CT, USA]),¹⁴ and tocilizumab (RoActemra® [Roche, Basel, Switzerland])¹⁵ in the European Union, and infliximab (Remicade®)¹⁶ and pegvisomant (Somavert® [Pfizer Inc, New York, NY, USA])¹⁷ in the United States.

Regarding the 13 products that have been approved by both the EMA and the FDA, PMS activities including RWD are generally similar, both suggesting or requiring collection of information on overall safety of products or pregnancy-related outcomes. There are certain cases in which there are slight differences in the PMS data to be submitted to the regulators; for example, erenumab (Aimovig®), in which safety data on pregnancy are to be submitted to both regulators but additional RWD would also need to be submitted to the EMA on the number of migraine patients prescribed a migraine prophylactic drug, its pattern of use, and other cardiovascular events involving its use, among others.¹⁸ For Inotersen® (tegsedi), although both regulators note the use of an observational registry to collect information on overall safety and outcomes,^{19,20} the FDA also requests additional PMS activities focused on the establishment of a worldwide pregnancy surveillance program.

There are 3 identified cases in which there are differences between the 2 regulators, namely for patisiran (Onpattro®), pitolisant (Wakix®), and siponimod (Mayzent®). In the case of patisiran (Onpattro®) and pitolisant (Wakix®), PMS activities, including RWD submitted to the EMA, focus on collecting information on overall safety,^{21,22} whereas pregnancy outcomes are the focus of information submitted to the FDA.^{23,24} For siponimod (Mayzent®), the PMS activity for the EMA includes collecting RWD on pregnancy outcomes,²⁵ whereas the FDA focuses on RWD relating to specific patient cohorts and pediatric patients.²⁶

The aforementioned details trigger the interesting question to what extent, if any, there are instances when the 2 agencies are asking for similar data but the evidence sources are different and therefore the quality of data—and hence the basis for the decision-making—would be different. The granularity of our data does not allow us to elaborate on this subject, but we suggest it could be a topic for a separate study.

The Utility of Registries

Registries are valuable sources of data that are followed over time to support regulatory decision-making and can be regarded as organized systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or drug exposure.²⁷ Indeed, data drawn from registries are the most common RWD source as evidenced by our study and could reflect the normally high(er) data quality associated with this data type in which chance, bias, and confounding are limited and controlled.

We identified some products for which RWD were drawn from registries to support a postmarketing commitment. These include hemlibra (Emicizumab® [Genentech USA, South San Francisco, CA, USA]), lonsurf, tocilizumab (Roactemra®), insulin glargine (Semglee® [Mylan Pharmaceuticals Inc., a Viatris Company, Canonsburg, PA, USA]), and risankizumab (Skyrizi®), and several antiretroviral products such as doravirine (Delstrigo® [Merck Sharp & Dohme Corp, Kenilworth, NJ, USA]), atazanavir or cobicistat (Evotaz® [Bristol Myers Squibb Company, Princeton, NJ]), and tenofovir disoproxil (Tenofovir disoproxil Mylan®). In total, there were 104 products that used a registry to support a postmarketing commitment.

The utility of a registry-based study for a regulatory purpose depends on many factors related to its relevance to answer a specific research question, the characteristics of the concerned registry, the quality of the data collected, and the design and analytical plan of the proposed study.²⁸ They may be useful for evidence generation to supplement the evidence generated in the preauthorization phase, to evaluate the effects of medications received during pregnancy, or to provide data for postauthorization evidence generation. Bouvy et al²⁹ interrogated European Public Assessment Reports to identify products for which a request for a registry was made as a condition of the (initial) marketing authorization. All centrally authorized products that received a positive opinion from CHMP between January 1, 2005, and December 31, 2013, were included; of 392 products that received a positive CHMP opinion, 31 registries were requested for 30 products in total. Approximately two thirds (65%) were product registries, and one third (35%) were disease registries. As many as 71% of the registries had a primary safety objective, which is in concordance with our finding (79%).

McGettigan et al²⁸ concluded that registries are greatly underused in regulatory assessments. This is in concordance with Bouvy et al,²⁹ who reported that 30 products of a total of 392 (8%) between 2005 and 2013 used registries as a primary source of evidence but contrast with the present study in which 104 instances were identified in which registries were used in a total of 165 products (63%) in the time span studied (1998–2020). This could possibly be attributed to the fact that the inclusion of RWD in regulatory decision-making has gained traction in recent years.

Comparing RCTs With Observational Studies and the Generation of RWD

The FDA has commissioned and funded a project to assess the feasibility of predicting the outcome of (Phase IV) RCTs with RWD with the aim to support their internal decision-making processes.³⁰ In a publication from that study, it was suggested that although many questions on the effectiveness of medications can only be reliably assessed through an RCT, some questions could potentially be reliably answered by using RWE generated from nonrandomized database studies.³¹ Franklin et al³² reported on trial emulations and concordance between RCT and RWE findings and proposed that there is a need to conduct more trial emulations to understand how often and in what contexts RWE findings match RCTs.

EMA has also communicated on the topic, and Eichler et al³³ proposed that RCTs will remain the best available standard in many circumstances but could be complemented by other methodologies to address research questions in which traditional RCTs may be unfeasible or unethical. They elaborated on the feasibility of substituting RCTs with RWD analyses and argue that such approaches have to be validated by comparing the outcome of an RCT with that of the RWD analysis. They also argue that the results of the RCT must not be available when the RWD analysis is conducted to limit any potential bias and to avoid design and analysis choices being tuned to match the outcome of the RCT. We observe that this approach would not allow for the substitution of an RCT with an RWD analysis but rather constitute an add-on study on top of the standard RCT. This approach would hence add complexity to the development of new drugs and their characterization rather than supporting the introduction of novel stand-alone or complementary approaches. We do not necessarily believe there is

a need to establish an association between RCTs and RWE to face the future challenges in evidence generation. We think that both methods independently have a role to play in the regulatory armamentarium, depending on a number of considerations, including the research question being evaluated, the patient cohort, the intervention (and potential comparator), the study length, and the expected outcome.

The Future of Evidence Generation

The FDA has pioneered RWD/RWE through the Sentinel initiative, which went from pilot phase into full production in the 2014/2016 time frame, with the aim to develop a medical product safety surveillance system using existing data, and has become a leading evidence-generation platform. Sentinel proactively monitors medical product safety, provides for methodologic innovation, and serves as a platform to advance the science of RWE. It has the potential to catalyze meaningful change in the health care ecosystem, including the use of RWD in drug development.^{34–36}

The EMA expertise on the regulatory utility of RWD has similarly expanded significantly in recent years, as evidenced by the number of hosted workshops and trainings offered, published reports and papers, and issued guidelines. This includes the OPTIMAL (OPerational, TechnIcal, and MethodologICAL) project to explore the appropriate use of valid RWE for the regulatory purpose.^{3,37,38}

It is evident that RWD and RWE are receiving increased attention by drug regulatory authorities. Evidence is accumulating suggesting that properly designed and conducted RWD studies are suitable to support regulatory decision-making. We are convinced that as additional experience is garnered, the situations in which RWD can robustly and powerfully inform benefit–risk deliberations will mature and find a logical place in the regulatory tool kit.

CONCLUSIONS

The utility of RWD/RWE should not be underestimated as they have increasingly been used in recent years both for new product approvals and line extensions and in the postapproval setting to further document product features postlaunch, most notably the product safety profile.

RWD as a bona fide source in regulatory decision-making have undergone a major shift kindled by the growing access to high-quality RWD. Initially regarded

as a corroborative component to RCTs, there is now a growing appreciation of the potential of RWD as a source in its own right to support regulatory decision-making.

Our research lends evidence to the theory that RWD are a flexible and innovative means to generate actionable evidence that have become accepted by major regulatory authorities. RWD have become an essential and appropriate regulatory tool for decisions on the benefits and risks associated with clinical interventions.

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All authors are Sanofi employees and may hold shares and/or stock options in the company. All authors hold positions within the pharmaceutical industry, but they have not received any grant, honoraria, or other compensation to author the present paper. The study was conceived of, executed on, and written up in the course of the authors' daily job.

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