Use and potential of real-world data (RWD) and real-world evidence (RWE) to inform pre-market regulatory decisions: a scoping review.

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RWD136

BACKGROUND

The U.S. Food and Drug Administration (FDA) and other regulatory agencies are committed to advancing real-world data (RWD) and real-world evidence (RWE) use in regulatory decisions. The purpose of this review was to assess the current applications of RWD/RWE to clinical research, including novel methodology and study design, then determine the potential for using RWD/RWE to streamline pre-market regulatory approvals for biosimilars and interchangeable biologics.

METHODS

Articles indexed in PubMed, EMBASE, CINAHL, Scopus, Web of Science, and the grey literature were identified using the following keywords: real-world data, real-world evidence, regulatory, FDA or Food and Drug Administration, EMA or European Medicines Association. There were no restrictions by date or countries where studies were conducted. Included articles were published in English and assessed RWD/RWE to address a regulatory need. Articles were excluded for the following reasons: informing clinical practice or population health; not healthcare or not human; describing vaccine development or use; no drug products included; basic science including pharmacokinetic or pharmacologic studies; randomized or non-randomized controlled trials not using RWD/RWE; economic analysis; engineering or manufacturing; post-marketing or pharmacovigilance studies, including pragmatic trials; data infrastructure development; reviews, commentaries, or editorials.

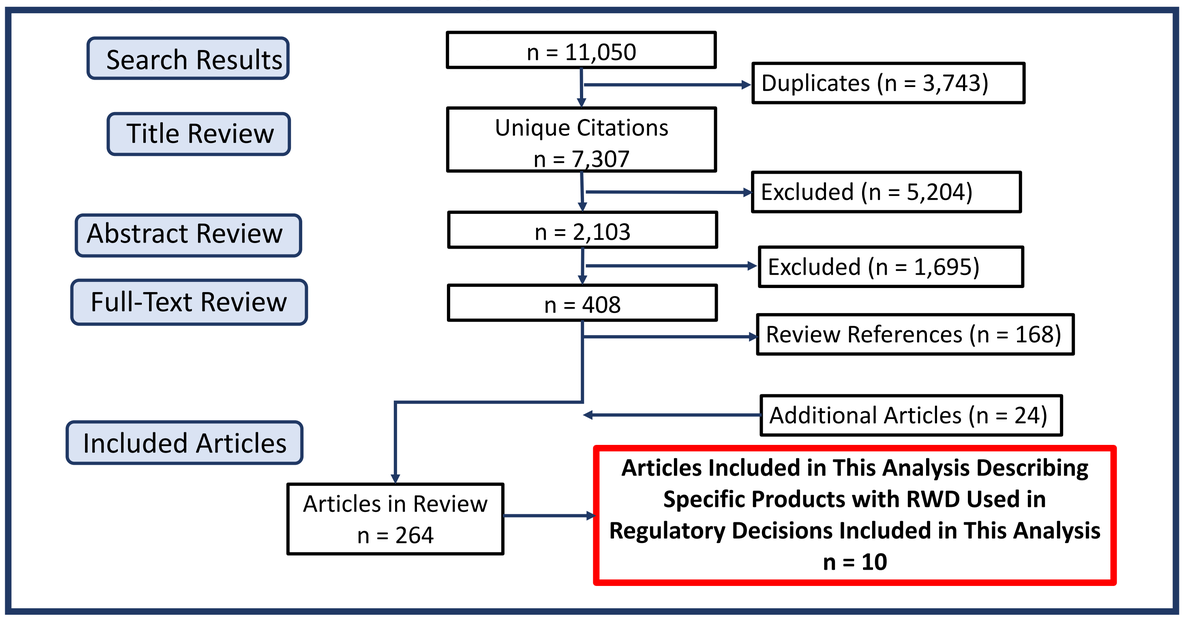
***Role of RWD – Definitions**

External Control: a control arm constructed from synthetic data or secondary data from patients not included in the clinical trial, typically contemporary to the study period
Historical Control: a control arm from patient data collected prior to the study period
Patient Natural History: assessment of disease processes using secondary data for untreated patients not in the clinical trial; similar to historical controls.
Expanded Access Program Data: data collected from patients treated prior to regulatory approval as a result of compassionate care or early-access programs

RESULTS

7,307 unique records were identified for screening (Figure 1). After title and abstract review, 408 were included for full-text review, including 168 articles that were reviewed for additional references. A total of 264 studies were included overall, with 10 included in this analysis. Table 1 describes products for which RWD/RWE were used in global regulatory applications.

Figure 1. PRISMA Diagram



****Agency**

F = US Food and Drug Administration (FDA)
E = European Medicines Agency (EMA)
J = Japan Pharmaceutical Manufacturers Association (JPMA)

Table 1. Global Product Approvals Including Real-World Data or Real-World Evidence in Regulatory Decisions

Approval**	Drug	Mechanism	Indication	Role of RWD*
1993[F]	clarithromycin	macrolide antibiotic	mycobacterium avium complex	expanded access program data
1997[F]	amphotericin B	antifungal	fungal infections	expanded access program data
1997[F] 2004[E]	anagrelide	platelet-reducing agent	essential thrombocytopenia	expanded access program data
1998[F] Withdrawn 2012[E]	lepirudin	recombinant hirudin	anticoagulant in patients with heparin-induced thrombocytopenia	control group registry data
2002[F] 2005[E]	nitisinone	tyrosine metabolism inhibitor	tyrosinemias	expanded access program data
2003[E] 2010[F]	carglumic acid	N-Acetylglutamate analog	hyperammonemia	retrospective review of data from N-acetylglutamate synthase-deficient patients
2005[F]	sodium phenylacetate/benzoate	antihyperammonemic	acute hyperammonemia in urea cycle disorders	expanded access program data
2006[F,E] 2007[J]	alglucosidase alfa	alpha-glucosidase analog	Pompe disease	external control
2012[F]	glucarpidase	recombinant carboxypeptidase g2	elevated methotrexate levels	expanded access program data
2013[E] 2015[F]	cholic acid	bile acid	inborn errors of bile acid metabolism	expanded access program data
2014[F]	elosulfase alfa	enzyme replacement	Morquio syndrome	characterize the biomarkers and disease manifestation
2014[F] 2015[E]	blinatumomab	bi-specific T-Cell engager (BiTE)	Philadelphia chromosome-negative relapsed and/or refractory B cell-precursor acute lymphoblastic leukemia	historical control
2015[F]	asfotase alfa	alkaline phosphatase	perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)	patient natural history
2015[F]	uridine triacetate	tri-acetylated uridine prodrug	hereditary oroticaciduria; fluorouracil or capecitabine overdose	expanded access program data
2016[F]	defibrotide	single-stranded oligonucleotides	hepatic veno-occlusive disease/sinusoidal obstruction syndrome	historical control
2016[E]	strimvelis	CD34+ enriched cell fraction	adenosine deaminase deficiency–severe combined immunodeficiency	control group from registry data
2016[F,E] 2017[J]	nusinersen	antisense oligonucleotide	spinal muscular atrophy	external cohort informed dosage and administration
Withdrawn 2017[E]	alipogene tiparvovec	gene therapy	lipoprotein lipase deficiency	characterize the biomarkers and disease manifestation
2017[F,E,J]	avelumab	anti-PD-L1	metastatic Merkel cell carcinoma	historical control
2017[F,E,J]	cerliponase alfa	enzyme replacement	neuronal ceroid-lipofuscinosis	external control
2017[E]	dinutuximab	GD2-binding monoclonal antibody	neuroblastoma	expanded access program data
2017[F]	selumetinib	mitogen-activated protein kinase inhibitor	neurofibromatosis type 1	patient natural history; data from the placebo-arm of the "failed" clinical trial for tipifarnib as comparison cohort
2017[F] 2018[E]	axicabtagene ciloleucel	CD19-directed T-cell immunotherapy	relapsed or refractory large B-cell lymphoma	external control
2017[F] 2018[E]	vestronidase alfa	beta-glucuronidase	mucopolysaccharidosis VII	expanded access program data
2018[F]	fish oil triglycerides	omega-3 fatty acid	parenteral nutrition-assisted cholestasis	expanded access program data
2018[F]	Lutetium lu177 dotatate	radiolabeled somatostatin analog	somatostatin receptor-positive (SSTR-positive) gastroenteropancreatic neuroendocrine tumors (GEP-NETs)	retrospective study of patients treated through expanded access program
2018[F,E]	tisagenlecleucel	CAR-T therapy	B-cell acute lymphoblastic leukemia	observational registry study
2018[E]	velmanase alfa	alpha-mannosidase	alpha-mannosidosis	expanded access program data
2019[F]	entrectinib	kinase inhibitor	ROS1-positive metastatic non-small cell lung cancer	external control using patients treated with crizotinib
2019[F,J]	erdafitinib	kinase inhibitor	locally advanced or metastatic urothelial carcinoma	external control with standard of care
2019[F]	polatuzumab vedotin-piiq	CD79b-directed antibody-drug conjugate	relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	put trial results in context
2019[F,J]	selinexor	exportin 1 inhibitor (small molecule)	relapsed or refractory multiple myeloma	historical control with EHR data
Withdrawn 2019[E]	zalmoxis	allogenic t-cell	adjunctive treatment in haploidentical hematopoietic stem cell transplantation of adults with high-risk hematological malignancies	control group from registry data
2020[F]	avapritinib	kinase inhibitor	unresectable or metastatic GIST with PDGFR-alpha exon 18 mutation	patient natural history
2020[F]	capmatinib	tyrosine kinase inhibitor	metastatic NSCLC with mutation leading to MET exon 14 skipping	patient natural history
2020[F]	tafasitamab	anti-CD19	relapsed or refractory DLBCL	external, historical control arm
2020[F]	tazemetostat	EZH2 inhibitor	metastatic or locally advanced epithelioid sarcoma	patient natural history
2020[F]	tazemetostat	EZH2 inhibitor	relapsed or refractory follicular lymphoma with EZH2 mutation	external control with standard of care

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CONCLUSIONS

- RWD has been used occasionally in regulatory decisions for new drug products, and primarily as external/historical control arms for single-arm trials for rare diseases. RWD has the potential to improve the efficiency of regulatory approval
- Only products specifically described in the literature were included in this analysis
- Some products known to include RWD in approvals were not described specifically in the literature and were not included in this analysis