A Systematic Review of Real-World Evidence (RWE) Supportive of New Drug and Biologics License Application Approvals in Rare Diseases

HPR111

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BACKGROUND

- Real-world evidence (RWE), defined as the clinical evidence derived from real-world data (RWD), reflects patient's health state and/or delivery of healthcare information that is collected from sources such as electronic health records (EHRs), medical/pharmacy claims and billing activities, product and disease registries, and cross-sectional surveys[1]
- RWE presents potential to contextualize and/or supplement traditional randomized controlled trials (RCTs) for regulatory approval of rare diseases (RDs), where it can be challenging to develop robust clinical evidence due to the smaller patient population, limited knowledge of natural history of the disease, or impracticality of conducting an RCT due to feasibility or ethical concerns[2,3]
- The 21st Century Cures Act of 2016 in the United States expanded the scope of utilizing RWE beyond the context of postmarket surveillance, which has potentially accelerated the use of RWE in US Food and Drug Administration (FDA) regulatory submissions[1,3]

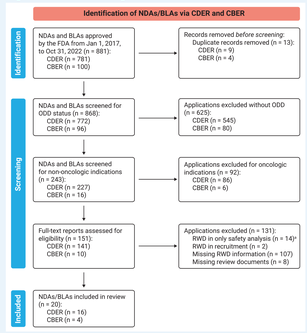
OBJECTIVES

- To conduct a systematic literature review (SLR) of new drug applications (NDAs) and biologics license applications (BLAs) submitted to the FDA, aiming to:
  - Review the use of RWD for efficacy outcomes in regulatory submissions for RD therapies
  - Evaluate the FDA's feedback on the submitted RWD

METHODS

- An SLR of NDAs and BLAs submitted between January 2017 and October 2022 was conducted; submission packages were obtained from publicly available FDA drug approval bodies (Center for Drug Evaluation and Research [CDER][a] and Center for Biologics Evaluation and Research [CBER][b])
- Approvals with orphan drug designation (ODD) were screened. Subsequently, applications for non-oncologic RD therapies were manually reviewed using RWE-related keywords
- NDAs and BLAs for RD therapies using RWE to support efficacy outcomes were included in the review, excluding applications using RWD for safety outcomes or recruitment
- 2 authors independently conducted the screening, while discrepancies were resolved through review discussions with all authors. Data extraction was performed by 1 author and quality was checked by another

Figure 1. PRISMA Diagram



BLA, biologics license application; CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; FDA, US Food and Drug Administration; n, number of approvals; NDA, new drug application; ODD, orphan drug designation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RWD, real-world data.

*Number of applications with the use of RWD for safety analysis included in the application packages, without accounting for applications with prospective, postmarketing safety registry/data plans.

PRISMA diagram template was adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

RESULTS

Application Characteristics of NDAs and BLAs

- A total of 868 applications (772 NDAs, 96 BLAs) were screened for non-oncologic RDs; 151 applications were subsequently reviewed for the RWD used to support efficacy outcomes. Of these, 20 (12 NDAs, 8 BLAs) applications for RD therapies with ODD were included in the review (**Figure 1**)
- 17 applications (85%) went through priority reviews compared with 3 applications (15%) for standard reviews. 3 therapies (15%; Skysona [elivaldogene autotemcel], Viltepso [viltolarsen], and Voxzogo [vosoritide]) received accelerated approvals. 6 of the approved medications (30%) were indicated for neuromuscular and bone-related disorders, while 5 (25%) were approved for rare metabolic disorders (**Table 1**)

Table 1. Application Characteristics of Approvals

Therapy, brand (generic)	Approved indication	NDA/ BLA	Review type	Approval date
Skysona (elivaldogene autotemcel)	Early cerebral adrenoleukodystrophy (CALD)	BLA	Priority	Sept 16, 2022[a]
Amvuttra (vutrisiran)	Polyneuropathy of hereditary transthyretin mediated amyloidosis in adults	NDA	Standard	Jun 13, 2022
Voxzogo (vosoritide)	Increase in linear growth in children with achondroplasia ages 5 and older with open epiphyses	NDA	Priority	Nov 19, 2021[a]
Rethymic (allogeneic processed thymus tissue-agdc)	Immune reconstitution in pediatric patients with congenital athymia	BLA	Priority	Oct 8, 2021
Nulibry (fosdenopterin)	Molybdenum cofactor deficiency (MoCD) type A	NDA	Priority	Feb 26, 2021
Zokinvy (lonafarnib)	Hutchinson-Gilford progeria syndrome (HGPS) and processing deficient progeroid laminopathies (PL)	NDA	Priority	Nov 20, 2020
Viltepso (viltolarsen)	Duchenne muscular dystrophy	NDA	Priority	Aug 12, 2020[a]
Evrysdi (risdiplam)	Spinal muscular atrophy	NDA	Priority	Aug 7, 2020
Dojolvi (triheptanoin)	A source of calories and fatty acids in the treatment of long-chain fatty acid oxidation disorders (LC-FAOD)	NDA	Standard	Jun 30, 2020
Pretomanid (pretomanid tablet)	Pulmonary extensively drug-resistant (XDR) and treatment-intolerant/ nonresponsive (TI/NR) multidrug-resistant (MDR) tuberculosis in adults	NDA	Priority	Aug 14, 2019
Zolgensma (onasemnogene abeparvovec-xioi)	Spinal muscular atrophy (SMA)	BLA	Priority	May 24, 2019
Egaten (triclabendazole)	Fascioliasis	NDA	Priority	Feb 13, 2019
Diacomit (stiripentol)	Dravet syndrome	NDA	Priority	Aug 20, 2018
Omegaven (fish oil triglycerides inj. emulsion)	Parenteral nutrition-associated cholestasis (PNAC)	NDA	Priority	Jul 27, 2018
Crysvita (burosumab)	X-linked hypophosphatemia (XLH)	BLA	Priority	Apr 17, 2018
Luxturna (voretigene neparvovec)	Biallelic RPE65 mutation-associated retinal dystrophy	BLA	Priority	Dec 19, 2017
Hemlibra (emicizumab-kxwh)	Hemophilia A (congenital factor VIII deficiency)	BLA	Priority	Nov 16, 2017
Mepsevii (vestronidase alfa-vjbk)	Mucopolysaccharidosis type 7 (MPS VII)	BLA	Priority	Nov 15, 2017
Brineura (cerliponase alfa)	Neuronal ceroid lipofuscinosis type 2 (CLN2)	BLA	Priority	Apr 27, 2017
Tepadina (thiotepa)	Class 3 β-thalassemia	NDA	Standard	Jan 26, 2017

BLA, biologics license application; NDA, new drug application.
[a]Accelerated approval.

Characteristics of RWD Used in FDA Review Packages

- Most applications (18; 90%) used only retrospective RWD, while the remaining 2 applications (10%) collected RWD both retrospectively and prospectively. RWD included RD registries (2; 10%), natural history/historical control (12; 60%), medical chart reviews (4; 20%), and external controls from other studies (2; 10%; **Table 2**)
- 3 (15%) used RWD for contextualization, 10 (50%) used it for comparison, while 7 applications (35%) used RWD for both contextualization and comparison
- 12 applications (60%) matched duration of RWD with trials' duration, and 13 (65%) included a priori protocol, as the FDA highly recommends prior discussion of protocol and study design development with the agency
- 17 applications (85%) reported matching patient eligibility criteria; however, the FDA commented on differences in patient population and/or missing information on key elements for 10 products (50%)
- All applications (20; 100%) reported RWD study sample sizes, which were varied, mainly depending on the prevalence and rareness of the disease and ranged from 10 in Study CL002 of Mepsevii (vestronidase alfa-vjbk) to 559 for the matched natural history cohort at baseline for Voxzogo (vosoritide)
- Only 3 applications (15%; Amvuttra [vutrisiran], Voxzogo [vosoritide], and Omegaven [fish oil triglycerides inj. emulsion]) reported methods for handling bias and missing data, whereas 17 products (85%) did not report methods to handle missing data and 5 (25%) reported methods for handling only bias
- 9 applications (45%) received overall positive feedback from the FDA on RWD considering the large effect size, appropriateness and justifiable RWD design, and/or use of RWD as external controls; although some of the applications had noticeable differences in baseline characteristics, and/or selection bias/measurement errors, which did not seem to affect analyses or effect size
- The FDA criticized 11 applications (55%) on RWD due to differences in patient population, potential selection bias and measurement errors, imprecision of population matching, missing information on key elements/input, or potentially subjective elements of definitions

Table 2. Characteristics of RWD Used in FDA Review Packages

Therapy, brand (generic)	RWD study design	Temporality: Retrospective/ Prospective/Both	Purpose: Contextualization/ Comparison/ Both	RWD study sample size	Duration matches trial	A priori protocol	Eligibility criteria matched	Methods for bias or missing data reported	FDA feedback
Skysona (elivaldogene autotemcel)	Natural history	Retrospective	Both	172	✗	✓	✓	✗	• Overall population not comparable to trial population • Potential selection bias and missing data • Potentially subjective elements of definitions
Amvuttra (vutrisiran)	External placebo control	Retrospective	Comparison	77	✓	✓	✓	✓	• Notable differences in baseline patient characteristics and disease severity compared to trial • Large effect size was sufficient to overcome potential biases and support efficacy outcomes
Voxzogo (vosoritide)	Natural history	Retrospective	Comparison	Matched at baseline: 559; Matched at 5 years: 360	✓	✓	✓	✓	• Limited data on genetic diagnosis, medical history, medications; but unlikely to skew results in favor of vosoritide • Measurement errors were not expected to have a significant impact on analyses
Rethymic (allogeneic processed thymus tissue-agdc)	Natural history	Retrospective	Comparison	49	✓	✓	✓	Bias: ✓ Missing data: ✗	• Missing information on phenotypes, underlying genetic defects, comorbidities, supportive care • Consistent large survival effects, with a favorable benefit-risk profile in patients
Nulibry (fosdenopterin)	Natural history	Both	Both	Retrospective: 37; Prospective: 14	✓	✓	✓	Bias: ✓ Missing data: ✗	• Potential for selection bias was adequately overcome; detection bias didn't impact observed survival benefit
Zokinvy (lonafarnib)	Registry	Retrospective	Comparison	Unmatched: 81; Matched: 62	✗	✗	✓	Bias: ✓ Missing data: ✗	• Differences in number of patients among cohorts; treated cohort had a substantially higher censoring rate over time than the matched untreated cohorts • Missing data on concomitant cardiovascular medications in control arm
Viltepso (viltolarsen)	Natural history	Retrospective	Comparison	69	✓	NR	✓	Bias: ✓ Missing data: ✗	• Heterogeneity of the disease, patient characteristics, care • Imprecision of population matching due to lack of control of all known and unknown biases
Evrysdi (risdiplam)	Natural history	Retrospective	Both	Prior NH study Finkel 2014: 79; DeSanctis 2016: 33; Kolb 2017: 26	NR	NR	✓	✗	• Considers the external natural history control as sufficient • NH of SMA is well understood
Dojolvi (triheptanoin)	Medical chart review	Retrospective	Comparison	29	CL201: ✓ CL202: ✗	✗	✓	✗	• Heterogeneity in disease severity, dietary management, data collection of lab and major clinical events • Dietary details missing for many patients, prior treatment history not properly collected or accounted for in analysis
Pretomanid (pretomanid tablet)	Historical control	Retrospective	Both	202	✗	✓	✓	Bias: ✓ Missing data: ✗	• Similar baseline characteristics, but trial patients had much greater rates of treatment success and lower mortality rates compared with historical control
Zolgensma (onasemnogene abeparvovec-xioi)	Natural history	Retrospective	Comparison	23	NR	✓	✓	✗	• NH results indicated that the expected treatment effect is large, readily ascertained, and shows close temporal association with the intervention
Egaten (triclabendazole)	Historical control	Retrospective	Comparison	37	✓	✓	NR	✗	• Large treatment effect was observed compared with the historical control
Diacomit (stiripentol)	Medical chart review	Retrospective	Both	29	✗	✗	✓	✗	• Methods are not powered to detect significant effects
Omegaven (fish oil triglycerides inj. emulsion)	Natural history	Retrospective	Both	Study 34: PP, 52; PM, 26 Study 35: PP, 24; PM, 15	✓	✓	✓	✓	• Covariate measurement errors, unmet model assumptions, biases in endpoint estimates
Crysvita (burosumab)	Natural history	Retrospective	Both	52	✓	✓	✓	Bias: ✓ Missing data: ✗	• NH study and trial results provide support for the effectiveness of burosumab therapy
Luxturna (voretigene neparvovec)	Medical chart review	Retrospective	Contextualization	70	✓	✗	✓	✗	• Chart review contextualized natural history of retinal dystrophy including many mutations and a variety of clinical diagnoses
Hemlibra (emicizumab-kxwh)	External control	Retrospective	Contextualization	Cohort A: 103; Cohort B: 24; Cohort C: NR	NR	✓	NR	✗	• Superiority over other products has not been proven, and results should be interpreted with caution • Note: RWD was used only for contextualization
Mepsevii (vestronidase alfa-vjbk)	Medical chart review	Both	Contextualization	Study CL001: 50; Study CL002: 10	NR	NR	✓	✗	• No clinical examinations were completed, and degree of cognitive disability appeared to be underestimated in noninterventional studies, which could impact endpoint selection, completion, and interpretation
Brineura (cerliponase alfa)	Registry	Retrospective	Comparison	69	✓	✓	✓	✗	• Differences in clinician-reported outcomes used to compare disease progression in both arms
Tepadina (thiotepa)	Historical control	Retrospective	Comparison	71	✓	✓	✓	✗	• Patient demographics were generally similar at baseline, except for history of splenectomy • Justifiable study design as an RCT could not be blinded and enrollment would be impractical due to rarity of the disease

FDA, US Food and Drug Administration; NH, natural history; NR, not reported; PM, pair-matched population; PP, per-protocol population; RCT, randomized controlled trial; RWD, real-world data; SMA, spinal muscular atrophy.
Note: Green highlighted rows represent positive FDA feedback; red X's denote no; green check marks denote yes.

Limitations

- This SLR was limited to publicly available information on non-oncologic RD applications approved by the FDA
- The FDA's review process varied by application, which was mainly influenced by the rareness of disease, rationale for RWD usage, quality of RWE study design components, and other such contributing factors. Hence, it was not possible to draw a definitive pattern to strongly recommend RWD design methodology for RD regulatory submissions, and rather provided key themes and considerations to implement in an assessment or application of use of RWD in support of RDs toward regulatory submissions

CONCLUSIONS

- This SLR reviewed how RWD were used for disease contextualization and/or efficacy comparison for RD therapies within FDA submissions since the enactment of the 21st Century Cures Act in 2016
  - It showed that FDA RD submissions with a large effect size were generally accepted despite noted concerns and criticisms
  - The FDA clearly criticized RWD study designs for differences in baseline characteristics of population, handling bias, and missing information in RWD
  - Other key themes were less clear, but included RWD design, potential selection bias and measurement errors, imprecision of population matching, or potentially subjective elements of definitions
- This review serves to inform future researchers and applicants on the FDA's comments and concerns and to focus on key areas to strengthen the use of RWD, to appropriately contextualize and compare with trial populations, to derive the unbiased effect size of intervention, and to appropriately support evidence packages to regulatory submissions
- As the use of RWD in regulatory applications is increasing, there is an opportunity to improve both the understanding of the FDA's expectations for utility and quality of RWD, as well as the applicants' adherence to such expectations

ABSTRACT PLAIN LANGUAGE SUMMARY

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Disclosures

GB and VS are employees of Moderna, Inc., and hold stock/stock options in the company. SV is an employee of HealthEcon Consulting, Inc., and an external consultant for Moderna, Inc. KAT is a PhD candidate at Auburn University and was a summer intern at Moderna, Inc., during the review.

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