Lessons Learned from Successful Real-World Evidence (RWE) Studies Supporting Regulatory Drug Approvals

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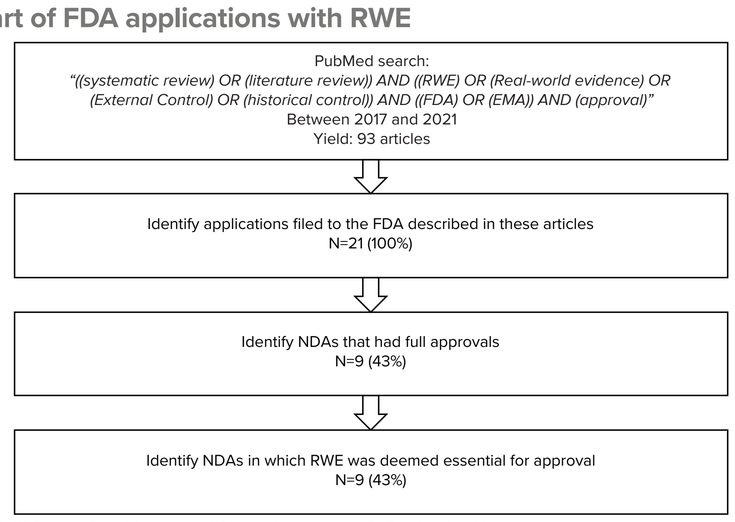
INTRODUCTION

- The use of real-world evidence (RWE), gleaned from real-world data (RWD) including electronic health records (EHR), patient-generated data, and data from disease or product registries, has become increasingly important to the Food and Drug Administration (FDA) in supporting the approval of new drug applications (NDAs) and biologics license applications (BLAs)[1-4]
- RWE can be used to help achieve fast-track drug approval in cases of rare diseases with urgent need but fewer patients, new indications for existing drugs, or as external controls in cases where placebo-controlled trials are difficult to conduct due to ethical considerations
- In 2018 and 2021, the FDA created guidelines for using RWE in clinical research,[3,4] however, there is limited information about how RWE has been used in successful applications[1,2]
- This study reviewed successful drug applications to shed light on how the FDA considers RWE when reviewing applications for new drugs

METHODS

- A search on PubMed was conducted to identify literature between the years 2017 and 2021 that reviewed or evaluated successful FDA/EMA approvals using RWE (**Figure 1**)
- Using publicly available information including submission packages, FDA briefing documents, and multidisciplinary reviews, documents were reviewed for each FDA approval
- These applications were analyzed for factors that were considered during the FDA's review of the application, including clinical trial efficacy endpoints, RWE endpoints, drug toxicity profiles, mechanism of action, non-oncology outcomes, needs of the disease population, and statistical methods
  - The applications were also analyzed for basic characteristics, including therapeutic area, indication type, the active arm data source, the control arm data source, and clinical endpoints
- For cases in which the FDA deemed RWE essential for approval, the attributes were summarized

Figure 1. Flowchart of FDA applications with RWE



EMA, European Medicines Agency; FDA, US Food and Drug Administration; NDA, new drug application; RWE, real-world evidence.

RESULTS

- Several FDA approvals were identified in which RWE was deemed essential
  - Examples included lutetium Lu 177 dotatate (Lutathera™) and avelumab (Bavencio™) in oncology, and cerliponase alfa (Brineura™) in neurological disorders (**Table 1**)
- The cases spanned wide therapeutic areas, including hematologic disorders, oncology, neurological disorders, and digestive disorders (**Figure 2**)
- The endpoints the FDA considered for approval included progression-free survival, overall response rate, laboratory blood tests, or others (**Figure 3**)
- While most of the applications used randomized clinical trial (RCT) data for the active arm, almost all used RWE as controls (**Figure 4**)
- The FDA acknowledged the use of response outcomes (eg, overall response rate and duration of response) assessed by the Independent Review Committees (IRCs) as oncology real-world endpoints
  - In solid tumor studies, the FDA generally did not consider RWE using outcomes that were not aligned with Response Evaluation Criteria in Solid Tumors (RECIST) criteria
- Real-world survival outcomes (eg, progression-free survival) were not recommended unless time zero was proved to be consistent with the corresponding clinical trial
- Non-oncology outcomes that evaluated discrete or acute events had a higher acceptance rate
- Factors frequently favored by the FDA in submissions using RWE included large effect size compared with historical threshold from RWE, the high unmet need of the disease population, improved drug toxicity profile, meaningful drug mechanism of action, well-defined real-world endpoints consistent with clinical trials, and proper use of statistical methods in matching baseline covariates in predefined protocols and statistical analysis plans

Table 1. Examples of NDAs Containing RWE

Compound	Indication	Year	Indication type	Active arm data source	Control arm data source	Clinical endpoints
Lutathera (lutetium Lu 177 dotatate)	Gastroenteropancreatic neuroendocrine tumors (FDA, 2018)	2018	rare disease	clinical trial (n=116) and expanded access program (n=360)	clinical trial (within same study, n=113)	PFS
Bavencio (avelumab)	Metastatic Merkel cell carcinoma (FDA and EMA 2017)	2017	rare disease	clinical trial (n=88)	electronic health record (n=14)	ORR
Brineura (cerliponase alfa)	Batten disease (EMA and FDA 2017)	2017	rare disease	clinical trial (n=22)	natural history database (n=48)	0 to 6 point motor-language CLN2 clinical rate decline

EMA, European Medicines Agency; FDA, US Food and Drug Administration; NDA, new drug application; ORR, overall response rate; PFS, progression-free survival; RWE, real-world evidence.

Figure 2. Therapeutic Area (n)

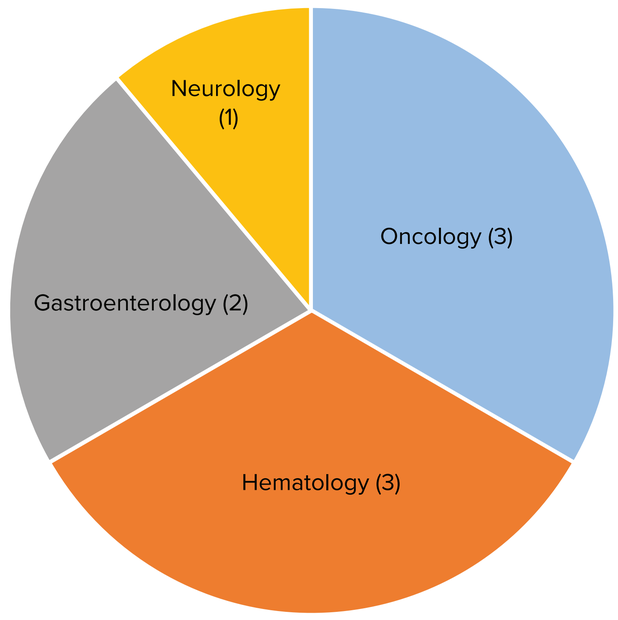
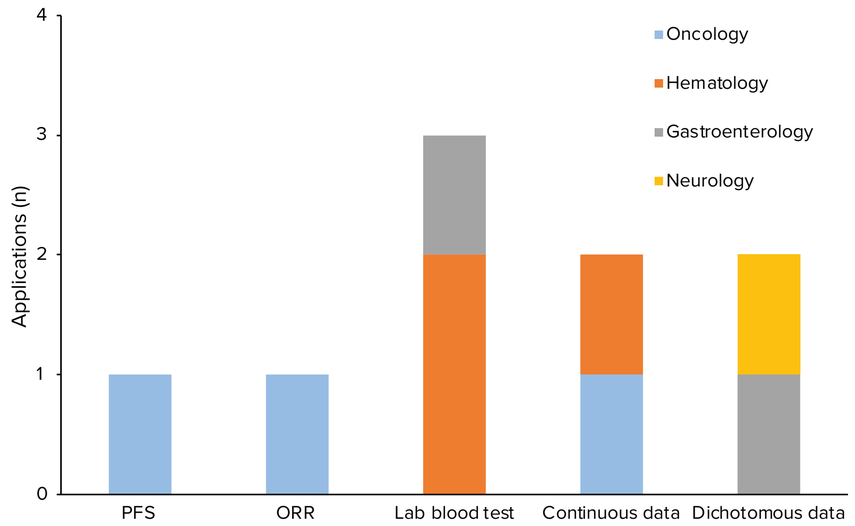
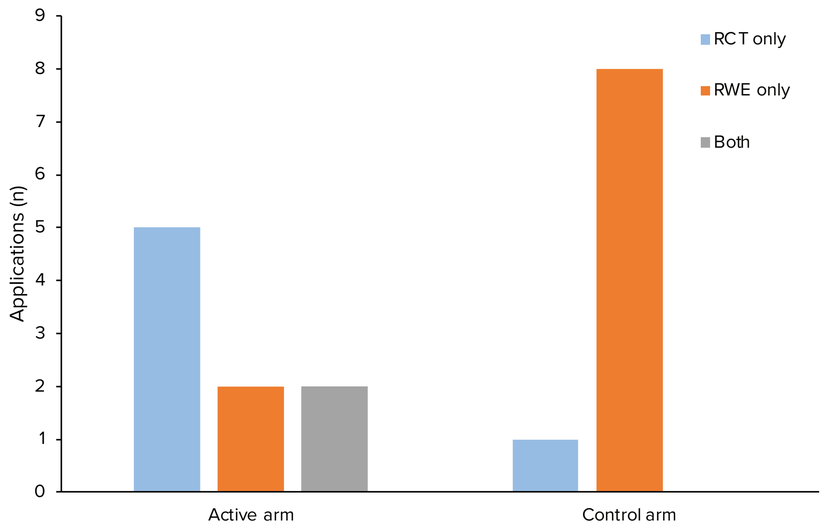


Figure 3. Clinical Endpoints from RWE



ORR, overall response rate; PFS, progression-free survival; RWE, real-world evidence.

Figure 4. Active Arm and Control Arm Data Sources



RCT, randomized clinical trial; RWE, real-world evidence.

CONCLUSIONS

- There was a limited number of NDAs in which the FDA deemed RWE essential for approval
- All successful applications that used RWE were for indications classified as either rare diseases or orphan diseases, and most were either hematologic diseases or related to oncology
- The clinical endpoints evaluated for approval varied, though most involved laboratory blood test evaluations
- FDA applications with RWE were more likely to be successful if RCT data were used for the active arm and RWE was used for controls
- Study design and drug and disease situations were the main factors in the FDA's acceptance using RWE
- It may help to engage early with the FDA in RWE study design
  - Statistical adjustments can greatly increase the scientific validity and robustness; however, this may not rescue all caveats in the study design

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ACKNOWLEDGMENTS

Editorial assistance was provided by Medical Expressions (Chicago, IL) and was funded by BeiGene, Inc.

DISCLOSURES

All authors are employees of BeiGene and may own stock in BeiGene.

Presented at ISPOR EU 2022, November 6-9; Virtual