EXAMINE THE USE OF REAL-WORLD EVIDENCE TO SUPPORT FDA DECISION-MAKING FOR NDA AND BLA FROM 2021 TO 2022

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INTRODUCTION

- The 21st Century Cures Act played a pivotal role in accelerating momentum for the use of real-world evidence (RWE) in regulatory decision making, which has led to significant changes in the regulatory landscape for incorporating RWE into the drug development process.[1]
- In recent years, FDA has been exploring RWE use to inform regulatory decision-making regarding drug's effectiveness, as mandated by Prescription Drug User Fee Act (PDUFA) VI and 21st Century Cures.[2]
- RWE can complement or serve as alternatives in instances where randomized controlled trials may not be practical or feasible, such as (1) prohibitive costs, (2) ethical concerns about administering a placebo, and (3) challenges in patient recruitment of rare disease.[3]

OBJECTIVE

- We aim to identify cases applying RWE in FDA approvals for New Drug Applications (NDAs) and Biologics License Applications (BLAs) and to understand the contribution of RWE in the US regulatory process.

METHODOLOGY

- To identify cases applying RWE, we reviewed NDA and BLA approvals from January 2021 to December 2022 in the Drugs@FDA database.
- Approvals for new molecular entities (NMEs) with NDA type 1 ("new molecular entity") and type 9 ("new indication or claim, drug not to be marketed under type 9 NDA after approval") were included based on FDA's classification system.[3]
- We examined RWE keywords through FDA review documents, including retrospective, observational, real-world, epidemiology, chart review, claims, electronic medical record, registry, and natural history.
- To classify how the applicant intended to make use of the RWE studies in the context of the application, we categorized each RWE study where it was explicitly stated.[3]

RESULTS

- 92% of NME cases (81 out of 88 cases) incorporated RWE in applications.
- 81 cases (92%) used RWE to support the therapeutics context, 10 cases (11.4%) used RWE to support effectiveness and 8 cases (9.1%) used RWE to support safety. (Figure 1).
- Most cases demonstrated the therapeutic context, such as disease prevalence, incidence or natural history, by using RWE from previous epidemiologic studies. A few of them conducted their retrospective studies.
- 12 cases (75%) received at least one designation from FDA, indicating their high unmet needs (Table 1).

FIGURE 1 INCLUSION OF FDA-APPROVED NDAS AND BLAS FROM 2021 TO 2022

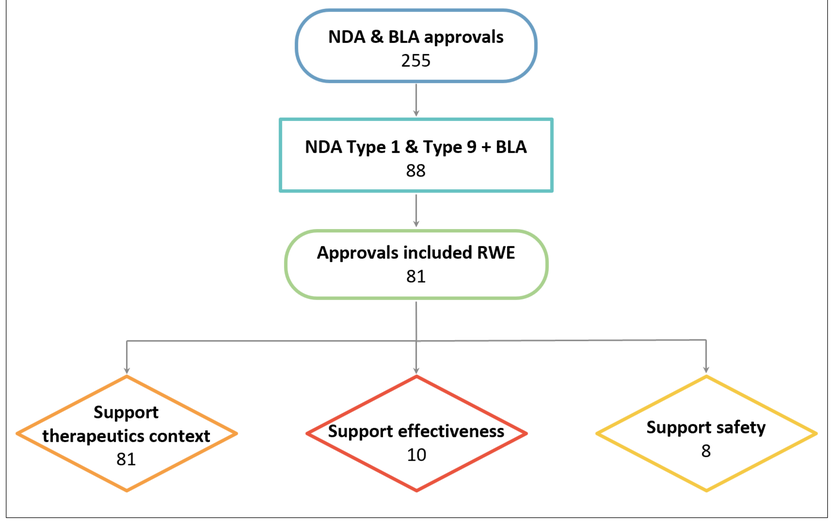
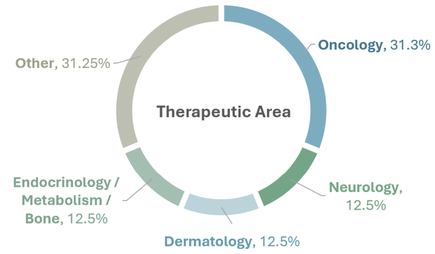


TABLE 1 16 CASES UTILIZED RWE TO SUPPORT EFFECTIVENESS OR SAFETY

	Supportive Effectiveness (n=10)	Support Safety (n=7)	Support Either (n=16)
Designation			
Priority review	6 (60%)	2 (28.6%)	7 (43.8%)
Orphan drug	9 (90%)	3 (42.9%)	10 (62.5%)
Breakthrough therapy	4 (40%)	3 (42.9%)	5 (31.3%)
Fast track	3 (30%)	0 (0%)	3 (18.8%)
Level of RWE			
Primary	1 (10%)	1 (14.3%)	1 (6.3%)
Supportive	6 (60%)	6 (85.7%)	12 (75%)
Not adequate for decision making	3 (30%)	0 (0%)	3 (18.7%)

FIGURE 2 THERAPEUTIC AREAS OF 16 CASES UTILIZED RWE TO SUPPORT EFFECTIVENESS OR SAFETY



- 10 cases that used RWE to support effectiveness demonstrated the natural history and disease patterns of the control group from RWE, which were indirectly compared to the effectiveness data in intervention groups, especially from single arm clinical trials.
- Common potential biases in RWE studies include: [4]
  (1) Selection bias or unobserved confounding (especially missing data on key covariates)
  (2) Different outcome assessment methods and frequency of measures compared with trials
  (3) Lack of comparability between external controls and trial populations
  (4) Misclassification of outcomes
  (5) Insufficient statistical methods for adjustment of differences between comparator groups

CONCLUSIONS

- In recent FDA's regulatory decision for NMEs, RWE have been incorporated into their submissions for diseases with high unmet needs.
- To support drug's effectiveness, RWE has been applied as an external control arm to compare with single-arm trials or as a description of the disease's natural history.
- However, it is crucial to address biases during the analysis to minimize potential harmful effects.

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