Successful Uses of Real-World Evidence in FDA Label Updates: A Descriptive Analysis of Regulatory Trends

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INTRODUCTION

- Real-world evidence (RWE) has become an increasingly important component of U.S. Food and Drug Administration (FDA) regulatory decision-making, particularly for post-approval label updates.[1]
- Statutory and policy initiatives, including the 21st Century Cures Act and the Framework for FDA's RWE, have formalized the agency's intent to incorporate real-world data (RWD) into regulatory evaluations.[2,3]
- Despite this growing emphasis, product sponsors continue to face uncertainty regarding the evidentiary characteristics of RWE that meet FDA expectations for label modifications.
- This study characterizes FDA regulatory decisions in which RWE supported approved label updates, examining trends over time and key evidentiary attributes to inform future RWE generation strategies.

OBJECTIVE

- To systematically describe FDA regulatory decisions in which RWE was used to support successful drug label updates.
- To characterize the key properties of FDA-accepted RWE studies, including study design, data sources, therapeutic modality and area, temporal trends, and regulatory context.

METHODS

- A descriptive analysis was conducted on FDA drug label update decisions in which RWE was cited to support the regulatory decisions.
- Data was obtained from the publicly available FDA webpage "FDA Use of Real-World Evidence in Regulatory Decision-Making," which summarizes regulatory decisions referencing RWE.[4]
- Variables captured included therapeutic modality, therapeutic area, RWD source, study design, and the regulatory role of RWE, with temporal trends in approvals evaluated descriptively.
- The regulatory role of RWE was classified as primary or supportive based on explicit language in FDA decision summaries describing its role in regulatory decision making. RWE was classified as primary when it served as the primary evidence base for a regulatory decision.
- Trial substitution level was classified as partial or minimal based on whether RWE supplemented or reduced reliance on traditional clinical trial evidence, without fully replacing trial data.

RWE CASES IDENTIFIED AND INCLUDED FOR ANALYSIS

57 Total RWE Cases Identified → **45** Drug & Biologic Label Change Records → **35** Confirmed Label Updates

10 Excluded
5 Publications
4 DSC (Drug Safety Communication)
1 PMR (Postmarketing Requirement Initiation)

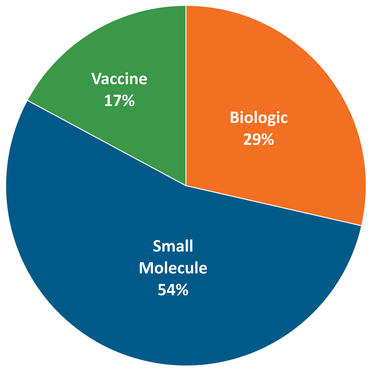
Of 57 FDA regulatory decision records referencing RWE, 45 involved drug or biologic label changes. After excluding non-label outcomes, 35 confirmed RWE-supported label updates were included in the analysis.

RWE regulatory role	n	%
Primary	25	71%
Supportive	10	29%

Trial Substitution Level	n	%
Minimal	9	26%
Partial	26	74%

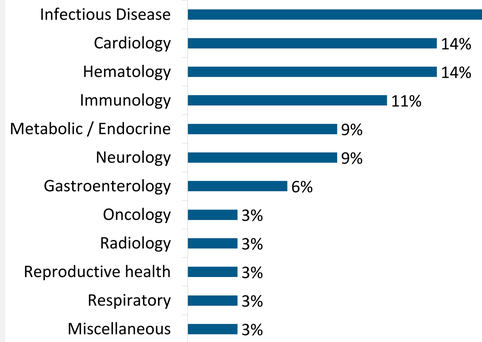
In most cases, RWE served a primary regulatory role (n = 25, 71%), directly informing FDA regulatory actions such as labeling or safety updates. Trial substitution was most often partial (n = 26, 74%), indicating that RWE primarily complemented existing clinical trial evidence rather than fully replacing it, with the remaining cases reflecting minimal trial substitution (n = 9, 26%).

FIGURE 1. DISTRIBUTION OF LABEL UPDATES BY THERAPEUTIC MODALITY



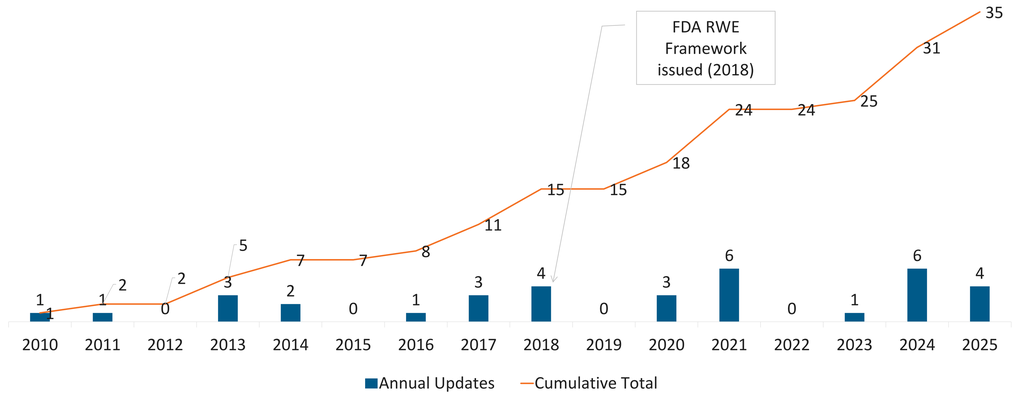
Small molecules represented the largest proportion of successful RWE-supported label updates (n = 19, 54%), followed by biologics (n = 10, 29%) and vaccines (n = 6, 17%).

FIGURE 2. RWE-SUPPORTED LABEL UPDATES BY THERAPEUTIC AREA



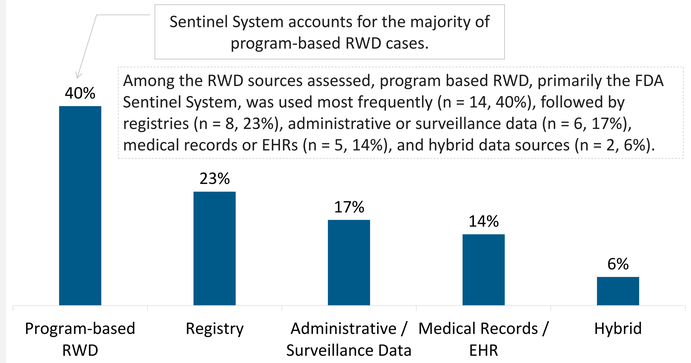
Infectious diseases represented the largest proportion of RWE-supported FDA label updates (n = 8, 23%). Cardiology (n = 5, 14%) and hematology (n = 5, 14%) were the next most frequently represented therapeutic areas, followed by immunology (n = 4, 11%). Neurology and metabolic/endocrine disorders each accounted for three label updates (n = 3, 9% each), while gastroenterology and other therapeutic areas were less commonly represented.

FIGURE 3. ANNUAL AND CUMULATIVE RWE-SUPPORTED FDA LABEL UPDATES



RWE-supported FDA label updates were limited prior to 2017 (cumulative n = 8). An increase in successful RWE-supported label updates was observed after 2017, coinciding with the publication of the FDA's Real-World Evidence Framework in 2018. The highest annual numbers were observed in 2021 and 2024, with six label updates in each year.

FIGURE 4. DISTRIBUTION OF REAL-WORLD DATA SOURCES



Among the RWD sources assessed, program based RWD, primarily the FDA Sentinel System, was used most frequently (n = 14, 40%), followed by registries (n = 8, 23%), administrative or surveillance data (n = 6, 17%), medical records or EHRs (n = 5, 14%), and hybrid data sources (n = 2, 6%).

FIGURE 5. STUDY DESIGN DISTRIBUTION AMONG RWE-SUPPORTED LABEL UPDATES

Retrospective cohort studies were the most frequently used study design (n = 13, 37%), followed by prospective registry studies (n = 8, 23%), descriptive studies (n = 7, 20%), and other study designs (n = 7, 20%). Overall, this distribution reflects the predominant study design patterns utilized across RWE-supported successful label updates.

CONCLUSION

- **RWE directly informed FDA regulatory actions such as labeling or safety updates in most cases. Trial substitution was usually partial, indicating that RWE complemented existing clinical trial evidence.**
- **Small molecules, followed by biologics and vaccines, represented the largest proportion of successful RWE-supported label updates. Infectious diseases led among therapeutic areas, followed by cardiology and hematology, with additional contributions from immunology, neurology, metabolic/endocrine disorders, and fewer cases in gastroenterology and other areas.**
- **Successful RWE-supported label updates increased markedly after 2017, coinciding with the FDA RWE Framework, with program based RWD sources, primarily the FDA Sentinel System, and retrospective cohort studies most frequently used.**
- **Due to the growing number of successful RWE-supported label expansions, manufacturers can begin outlining evidence generation strategies early in clinical development, which enables more efficient evidence planning and regulatory decision-making.**
- **However, this study is limited by reliance on publicly available regulatory documents, which may not capture all instances or nuances of RWE use. Future research should focus on assessing the quality and impact of different RWD sources and exploring FDA drug approvals that use RWE.**

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DISCLOSURES

NK, HD, and JK are employees of Axtria India Pvt. Ltd., Gurugram, India. RG and JM are employees of Axtria Inc., USA. CM is an employee of Axtria Inc., Canada. All authors declare no conflicts of interest related to this research.

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