RWD109

The Use of Real-World Evidence in FDA Regulatory Submissions: A Review

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Background & Methods

Real-world evidence (RWE) has played a growing role in supporting clinical trial designs and has increasing implications in regulatory decision-making for new and expanded indication approvals, coverage decisions, and post-market safety monitoring. In December 2018, the FDA issued a framework for the agency's RWE program[1]. The agency has since issued several guidance documents on types of RWE, considerations for using RWE to support regulatory decisions, and data standards for submitted real-world data (RWD)[2]. This review evaluated examples of RWE in regulatory submissions to the FDA following the issuance of the framework to provide a recent understanding of how RWE has been utilized to support new regulatory submissions and the resulting feedback from agency review.

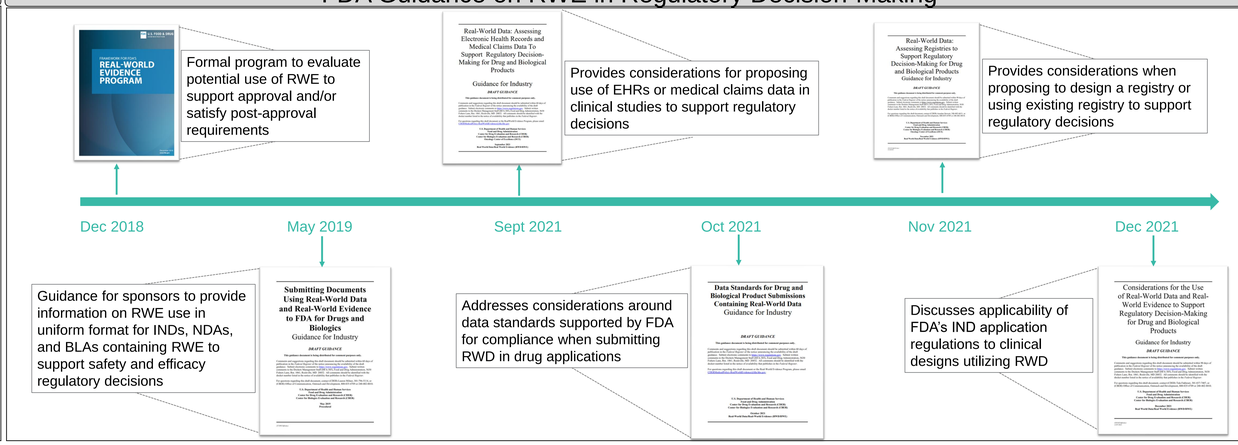
Potential benefits of RWD/RWE[1]

- Enables evidence development in settings where traditional randomized controlled trials (RCTs) are impractical to conduct
- Fills in gaps not typically addressed in RCTs (i.e., real-world use of products in patients with multiple comorbidities, long-term outcomes)
- Allows sponsors to generate evidence in support of an efficacy claim that is potentially more useful to patients and payers
- May significantly reduce time and cost of evidence development for some regulatory decisions

Methods

A targeted literature review was conducted to evaluate examples of regulatory submissions which used RWE in NDAs and BLAs reviewed and approved by the FDA between 2019 and 2021. Examples of new drug approvals and indication expansions were selected for analysis of RWE type, design, comparison to pivotal clinical trial, and FDA comment to determine whether RWE successfully contributed to the drug approval. The search included drugs from any therapeutic area but excluded examples of medical device approvals.

FDA Guidance on RWE in Regulatory Decision-Making[1,2]



Results: Case Studies of RWE Use in FDA Approvals[3,4]

Drug (approval date)	Regulatory Action	Type of RWD/RWE Used	FDA Review Takeaways
Tacrolimus (2021)	New indication approval: prevention of organ rejection in patients receiving lung transplant	Registry and mortality data as historical control for efficacy (retrospective cohort study)	• Well-designed study with detailed clinical data • Generalizable since registry data included almost all lung transplants in the US • Threats to validity: residual confounding, misclassification, selection bias
Abatacept (2021)	New indication approval: prevention of acute graft vs. host disease	Registry-based clinical study	• FDA noted incorporation of RWE as component of the determination of clinical effectiveness (included in approval press release that there are ongoing efforts to incorporate use of high-quality RWE in support of regulatory decision-making)
Avapritinib (2020)	New drug approval: adults with unresectable or metastatic gastrointestinal stromal tumors with a PDGRF-alpha exon 18 mutation	Chart review for contextualization	• Patient data were collected over a relevant time period for chart review • Data were collected only at centers where high-quality mutational analysis was done routinely to minimize the potential for confounding
Capmatinib (2020)	New drug approval: adults with metastatic non-small cell lung cancer whose tumors who have a mutation leading to *MET* exon 14 skipping	Global retrospective chart review of patients for contextualization of natural history of disease	• Data considered to be supportive, however, applicant did not submit RWD, so results could not be verified by the FDA • Provided an estimate of disease natural history • Applicant concluded RWE findings were clinically significant
Tafasitamab (2020)	New drug approval: with lenalidomide for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma	Retrospective observational cohort study conducted to generate matched control to main clinical trial	• Accuracy of results unclear given small sample size • Statements about 2 cohorts being balanced is difficult to substantiate • FDA does not agree that cohorts are representative of patients in target population
Selumetinib (2020)	New drug approval: pediatric patients, 2 years and older, with neurofibromatosis type 1 (NF1) and inoperable, plexiform neurofibromas	Data from natural history study and placebo-arm of failed trial for another drug as external control cohorts	• External control data considered to be supportive in a descriptive manner but inadequate for comparative analyses • Between-study differences in eligibility criteria, endpoint definition and assessment frequencies, and covariates
Palbociclib (2019)	Indication expansion: males with HR-positive, HER2-negative advanced or metastatic breast cancer	EHR and retrospective claims data to characterize use of Palbociclib in new patient population	• Criteria used to identify patients in cohorts do not guarantee comparability (matching and propensity scores not used) • Claims data should be interpreted with caution as groups were not balanced by age or stage of disease • New indication approval was based on submitted RWE alone
Selinexor (2019)	New drug approval: patients with relapsed refractory multiple myeloma (with dexamethasone)	EHR data from Flatiron Health database to use as comparison to single-arm trial	• Methodological issues with index date selection, comparability, immortal time bias; lack of prior protocol review from FDA → considered as a post hoc analysis • Post hoc strategies to increase comparability across cohorts were inadequate → limited sample size and unstable estimates
Entrectinib (2019)	New drug approval: adults with metastatic non small cell lung cancer whose tumors are ROS1-positive	EHR data from Flatiron Health database to approximate natural history of disease	• RWE arm unlikely to be generalizable and not sufficiently comparable to entrectinib clinical trial population • Significant differences in outcomes, favoring entrectinib arm • Analyses considered post hoc; FDA did not review initial protocol
Erdafitinib (2019)	New drug approval: adults with locally advanced or metastatic urothelial carcinoma	Natural history study using Flatiron-Foundation Medicine EHR data for contextualization of disease	• Several methodological issues → no definitive conclusion can be made / RWE not used in the decision • Unmeasured / missing confounders • Inconsistent exclusion criteria → differential selection of comparison groups & treatment misclassification
Polatuzumab vedotin-piiq (2019)	New drug approval: adults with relapsed or refractory diffuse large b-cell carcinoma	Literature review conducted for contextualization	• Literature places results of pivotal trial in context • Outcomes in pivotal trial raise question of underperformance of control arm
Onasemnogene abeparvovec (2019)	New drug approval: pediatric patients less than 2 years old with spinal muscular atrophy with bi-allelic mutations in the SMN1 gene	Natural history data to serve as an external control for single-arm study	• Comparison of results of Ph 3 clinical trial to available natural history data provides primary evidence of effectiveness • Natural history studies provided detailed characterization of disease in patient population
Pembrolizumab and Lenvatinib (2019)	Supplemental approval: advanced endometrial carcinoma that is not MSI-H or mismatch repair deficient	Previously conducted monotherapy clinical trial data to generate external control	• FDA conducted exploratory adjusted analyses and results were consistent, though results could be subject to residual unmeasured confounding • Results provided evidence for supplemental indication approval

RWE Highlights: Key Successes and Failures[3,5,6]

Tacrolimus (2021)

- Non-interventional study used **RWD** from the US Scientific Registry of Transplant recipients (SRTR) supported by Department of Health and Human Services
- Data collected on lung transplantation to support new indication approval; supplemented with evidence from RCTs in other solid transplant settings
- FDA noted the approval reflects "how a well-designed, non-interventional study relying on **fit for purpose RWD**, when compared with a suitable control can be adequate and well-controlled under FDA regulations"

FDA recommendations regarding labeling:

- Potential for residual confounding: avoid language presenting a comparative effectiveness claim between tacrolimus and other regimens
- Potential for exposure misclassification and selection bias: clearly word description of study population

Selinexor (2019)

- Retrospective, observational study using EHR data from Flatiron Health Database
- Goal: characterize survival of population similar to the one studied in single-arm trial to compare overall survival
- Protocol and SAP were not shared with FDA for review and consent; cannot confirm they were pre-specified.

Index date issues:

- Systematic differences in how the index date was defined across treatment arms could be potential source of bias.
- Original index dates induce immortal time bias in study results

Comparability issues:

- Original eligibility criteria to identify patients in database were different from clinical trial which limit comparability
- Differences may bias overall survival results in favor of trial population.

Selumetinib (2020)

- Natural history study of NF1 conducted to demonstrate key characteristic of disease
- Data from placebo arm of failed trial for another drug – feasible since the technique used to measure tumor response was identical
- No statistical comparisons were made
- FDA noted that plan to reference tumor volume data from natural history study and placebo arm was acceptable, but analyses would be exploratory
- External control data was considered supportive in a descriptive manner.

Inadequate for comparative analyses:

- Heterogeneity in patient population in disease, patient, and treatment characteristics
- Between-study differences including eligibility criteria and endpoint definition
- Lack of covariate information for external data

Conclusions

Thirteen examples of new drug approvals and indication expansions were selected through the literature search. Different sources such as registries, EHR data, and chart reviews were used within submissions. Other RWE sources included external control data from previously conducted clinical trials and natural history studies. The primary focus of FDA review was on how RWE was compared to or contextualized with the main clinical trial as well as how the RWD component was selected, designed, and analyzed using statistical methods.

Key Learnings:

- Using RWE can be especially useful in settings where the patient population is small (i.e., oncology and rare diseases) and when it may be unethical or not feasible to conduct a traditional RCT
- When approval is based on a single-arm interventional trial (mostly in oncology and rare diseases), supportive RWE has consisted of data on historical response rates drawn from chart reviews, expanded access programs, and other practice settings as an external control arm
- For studies using EHRs or medical claims data to support a regulatory decision, sponsors should submit protocols and statistical analysis plans prior to conducting the study; sponsors seeking FDA input before conducting the study should request comments or a meeting to discuss with the FDA review division[7]
- Limitations of external controls: difficulties in reliably selecting comparable population due to changes in medical practice, lack of standardized diagnostic criteria or equivalent outcome measures, and variability in follow-up procedures[1]
- Using registries as RWD can characterize natural history of a disease, provide information to help determine sample size, selection criteria, and study endpoints, select suitable study participants, identify biomarkers or clinical characteristics associated with key clinical outcomes, and support inferences about safety and efficacy[8]

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