RWE for Single and Well-Controlled Studies: An Evaluation of FDA Submissions for Effectiveness

Poster HPR52

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Background & Rationale

- Over the past 10 years, there has been accelerated use of real-world data (RWD) and real-world evidence (RWE) in drug development, both for safety and effectiveness.
- RWE contributing to effectiveness may be either supportive, such as background rates or describing treatment patterns, or substantial, such as the use of an external control arm in a pivotal single arm trial.
- Per 21 CFR 314.126, substantial evidence of effectiveness is generally met by two adequate and well-controlled studies. In certain circumstances, a single adequate and well-controlled clinical investigation together with another serving as confirmatory evidence can be sufficient.
- Real-world evidence (RWE) has been used to support regulatory decision-making for effectiveness—increasingly in the absence of two well-controlled studies; however, its use and acceptance as a single and well-controlled study versus confirmatory evidence has not been well characterized.

Objective: to characterize the use and acceptance of RWE as a single and well-controlled study versus confirmatory evidence, and to characterize trends in the use of these RWE in MAAs.

FDA regulations 21 CFR 314.126 outline the characteristics of an adequate and well-controlled clinical study

- **Substantial evidence of effectiveness** based on adequate and well-controlled clinical investigations is **required for approval** of a drug under section 505(c) of the Federal Food, Drug, and Cosmetic Act.
- In many cases, **two adequate and well-controlled** clinical investigations are needed.
- However, when scientifically appropriate, evidence from **a single adequate and well-controlled** clinical investigation with **one other study serving as confirmatory evidence of effectiveness** can be sufficient to meet the substantial evidence standard.

These can be externally controlled trials comparing a RW-arm to a trial arm, or a RW study with 1 or more RW arms

Role of RWE for effectiveness

- RWE that is the single adequate & well-controlled study
- RWE that provides confirmatory evidence

Methods

Study Design

- We conducted a review of marketing authorization applications (MAAs) containing RWE accepted by the FDA between January 2020-December 2025 for effectiveness.
- **Regulatory focus**: Food and Drug Administration (FDA) [US] due to their significant role in the regulatory landscape.

Automated Web Extraction

- A Python web-scraping script using was developed to extract all drugs (e.g., NDAs, sNDAs, BLAs, sBLAs) evaluated and approved by CDER and CDER.
- APIs from drugs@fda.gov, and metadata were scraped to extract PDFs including multidisciplinary reports.
- Reports were then scrapped for the presence of key words such as “natural history” and “external control”.
- Drugs were categorized based on:
  - Reviews available
  - Presence of RWD/RWE key words in any of the PDF reviews
  - RWE for safety were not evaluated.

Categorization & Analysis

- Multidisciplinary reports, including regulatory feedback, with key RWD/RWE hits were reviewed for MAAs containing RWE.
- Publicly available reports including DEPI and OBE reviews from CDER and CBER were reviewed.
- Two reviewers independently extracted the RWE, evaluated trial and RW study designs, and characterized the regulatory positioning of RWE:
  - **Substantial**: RWE provided the primary data & played a key role in decision-making
  - **Supportive**: RWE provided supplementary evidence
- Regulatory positioning of RWE was further categorized as:
  - **Adequate well-controlled study:** uses in effectiveness as primary evidence
  - **Confirmatory evidence:** used for effectiveness in supportive capacity
- Descriptive analyses were performed to identify trends in the characteristics of drugs and of the RWE.

Key Findings

- Among RWE submitted for effectiveness in single adequate well-controlled studies with confirmatory evidence, numerous were used as confirmatory evidence and also as part of single adequate and well-controlled clinical study.
- All medicines where RWE contributed to a single and well-controlled study were for orphan or ultra-orphan drugs, oncology/hematology, or rare diseases (data not shown).
- Common RW study designs for single well-controlled studies included external control arms (ECAs) compared to a trial arm, and retrospective cohort with historical controls. ECAs paired with trial data also served as confirmatory evidence, depending on the totality of evidence.
- Select MAAs solely relied on RWE as the primary evidence for single adequate and well-controlled investigations alone.

Why is this Research Important?

- This project looks at how RWE is used and classified by regulatory bodies when approving new drugs or drugs for new indications.
- We found that RWE is used for single adequate and well-controlled studies, either alone or as the RW arm contributing to the well-controlled study (e.g., ECA), and most often used in rare diseases and first-in-class drugs.
- This framework demonstrates a scalable approach for identifying, extracting and evaluating RWE methodologies within FDA reviews and may support future automation of regulatory evidence surveillance. In this instance manual review remained necessary to distinguish supportive from substantial evidence use.
- Given the various RWE use cases, companies may consider strategic integration of RWE into their evidence package, particularly for indications where randomized trials may be unfeasible.

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Results

Figure 1. Attrition Diagram for FDA CBER & CDER Drug Approvals Using Query Tool

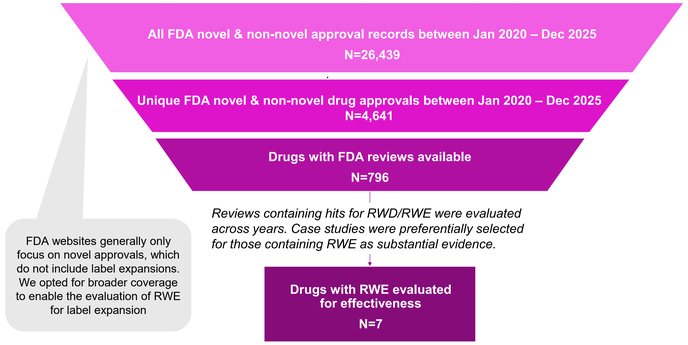


Figure 2. Characteristics of Drug Approval s from FDA.gov

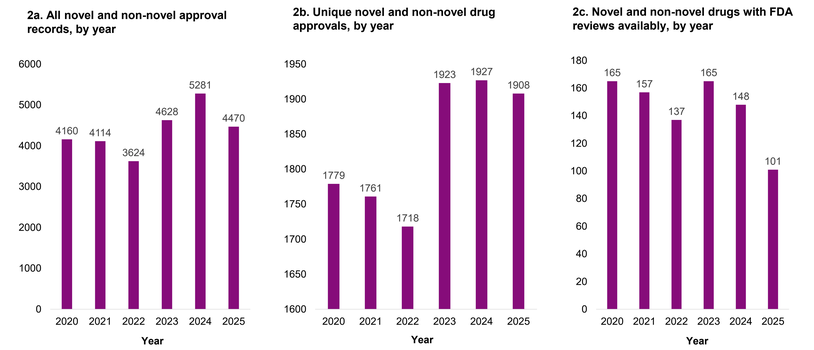


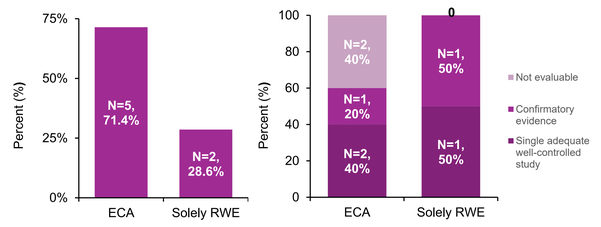
Table 1. Overview of selected medicines and RWE contributing to MAAs

Drug	Ide-cel	Tacrolimus	Alpelisib	Omaveloxolone	Palovarotene	Doxecitine and doxribtimine	Mirdametinib
Manufacturer	Bristol-Myers Squibb	Astellas Pharma, Inc.	Novartis	Biogen	Ipsen	UCB	SpringWorks Therapeutics
Indication	Relapsed/ refractory multiple myeloma	Rejection prevention for lung transplant	PI3KCA-related overgrowth spectrum (PROS)	Friedreich’s ataxia	Fibrodysplasia ossificans progressive FOP)	Thymidine kinase 2 deficiency (TK2d)	Neurofibromatosis type 1 (NF1)
Orphan Drug Status?	✓	✓	✓	✓	✓	✓	✓
RWE Study design	ECA with pivotal Ph2, SLR	Retrospective arm & historical comparator Registry‡	Retrospective single-arm study	ECA with pivotal Ph2	ECA with pivotal Ph3	ECA with pivotal Ph2 & RWD	ECA with pivotal Ph2
Data Source	EMR and Registry†	Chart review of EMRs	EMRs	Chart Review of EMRs	Retrospective chart review and individual patient data from published literature	Prospective study, used retrospectively	
Filing purpose	First indication	Expanded indication	Expanded indication	First indication	First indication	First indication	First indication
Application type	BLA	sNDA	NDA	NDA	NDA	NDA	NDA
Date Submitted	Jul 2020	Dec 2020	Oct 2021	Mar 2022	Feb 2023^	Dec 2024	Jun 2024
FDA Approval Date	Mar 2021	Jul 2021	Apr 2022	Feb 2023	Aug 2023	Oct 2025	Feb 2025
RWE Accepted?	No	✓	✓	✓	✓	✓	No (supportive only)
RW Type	N/A – not accepted	**Substantial evidence** of effectiveness: an **adequate and well-controlled study**^	**Confirmatory evidence** supporting effectiveness	**Confirmatory evidence** supporting effectiveness	**Substantial evidence** of effectiveness: an **adequate and well-controlled study**	**Substantial evidence** of effectiveness: an **adequate and well-controlled study**	N/A – not accepted

^ Complete response letter issued Dec 2022 with MAA resubmitted Feb 2023.
CNS = central nervous system, MM = multiple myeloma, NSCLC = non-small cell lung cancer, SLR = systematic literature review.
† Submission utilized RWD from multiple data sources including EMR and registry: clinical sites, Connect® MM Registry, Flatiron, GRN, M2Gen, and COTA.
‡ Scientific Registry of Transplant Recipients.

Figure 3. Study Designs of the RWE

ECA coupled with Pivotal Trial	Solely RWE
Ide-cel, w/ pivotal Ph2	Alpelisib – retrospective single-arm study
Palovarotene, w/ pivotal Ph3	Tacrolimus – retrospective arm & historical comparator
Omaveloxolone, w/ pivotal Ph2	
Doxecitine & doxribtimine , w/ pivotal Ph2 & RWD	
Mirdametinib, w/ pivotal Ph2	



ECA Acceptance

3 of the 5 ECAs were accepted by the FDA, 2 of which were post-hoc; 2 contributed to a single adequate and well-controlled study (palovarotene, doxecitine and doxribtimine).

- **Omaveloxolone**

Post hoc, propensity-score matched analysis comparing clinical trial extension data to a global 19-year natural history study.

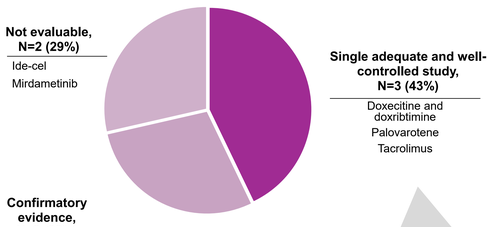
- **Paloveretene**

Propensity-score matched analysis comparing the single-arm Ph 3 to RW patients from a natural history study, comprised of FOP patients from sites, all of which were also used in the Ph3 study

- **Doxecitine and doxribtimine**

Propensity-score matched analysis comparing the treated patients from single-arm Ph 2 trial and retrospective data such as from compassionate use, to untreated RW patients from a natural history study and literature.

Figure 4. Classification of RWE as single adequate well-controlled study versus confirmatory evidence



RWE can be coupled with a clinical trial – such as in an ECA – or be the sole contributor of a single adequate and well-controlled study

Case Studies: RWE as sole clinical study

Tacrolimus
Single adequate and well-controlled study

- **Non-interventional study** of tacrolimus use assessed in routine clinical care
- **Data source**: United States STRT registry (see next slide)
- **Population**: patients in the registry who received single- or double-lung transplantation
- **Study period:** January 1, 1999 to December 31, 2017
- **Objective†:** evaluate the real-world effectiveness of tacrolimus + MMF in lung transplantation versus other regimens include CsA) + MMF and CsA + azathioprine
- **Endpoints**
  - Primary: 1-year all-cause mortality or graft failure (composite)
  - Secondary: 2- and 3-year all-cause mortality or graft failure (composite); mortality; graft failure; rejection^

RW Treatment Arm

Treatments: Tacrolimus + mycophenolate mofetil (MMF)

RW Control Arm

- **Comparators:**
  - Tacrolimus + azathioprine;
  - Cyclosporin A (CsA) + MMF;
  - CsA + azathioprine

Alpelisib
Confirmatory study

- **Non-interventional single arm study** of outcomes among PROS patients using alpelisib in routine clinical care
- **Data source**: chart review of alpelisib–treated PROS patients from 7 participating sites
- **Population**: Adult or pediatric patients of ≥ 2 of age with a physician confirmed/documented diagnosis of PROS, with documented evidence of a mutation in the PIK3CA gene.
- **Study period:** from index date up to data cut-off date March 09, 2020
- **Objective:** to assess response and clinical benefit of alpelisib (e.g., through change in lesions) among treated patients
- **Endpoints**
  - Primary: Response (y/n) at Week 24 or 6 months per BICR. Binary response was defined tumor reduction by ≥20%
  - Secondary^: Changes in sum of measurable target lesion, changes in sum of all measurable lesions, changes in sum of all measurable non-target lesions, and duration of response

RW Treatment Arm

Treatments: alpelisib

References: References are available upon request to the corresponding author at Shivani@landmarkscience.com; **E-poster and supplementary materials**: Copies of this poster and supplementary materials obtained through the QR code or link are for personal use only and may not be reproduced without permission;
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