eBook

The role of real-world evidence in FDA approvals

AETION®

DID YOU KNOW?

1 in 2

of 2019 approved FDA submissions for new drugs and biologics included a real-world evidence study.

Aetion generates decision-grade real-world evidence (RWE) for biopharma, payers, and regulatory agencies.

As industry prepares for the FDA's draft RWE guidance in 2021, we conducted a systematic review of FDA approval documents from 2019 to understand how RWE informs today's regulatory decisions.

This eBook will guide you through when, where, and how RWE studies have supported the approvals of New Drug Applications (NDAs) and Biologics License Applications (BLAs).

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HOW RWE STUDIES ARE USED IN FDA APPROVALS

In 2019, 49 percent of FDA-approved NDAs and BLAs included an RWE study. In 2020, that figure jumped to 75 percent.[1]

In 72 percent of submissions with an RWE study, the study influenced the FDA's approval decision.

"As we continue down the pathway regarding totality of evidence, RWE will continue to have a larger and larger role in evidence generation."

DR. AMY ABERNETHY

Principal Deputy Commissioner, FDA

Friends of Cancer Research: An International Framework for RWE

How RWE studies informed FDA decisions[2]

12%
Substantial evidence

60%
Supportive evidence

20%
Inconclusive

8%
Not addressed

RWE submission types[3]

In 2019, the following RWE study types were used to support safety and effectiveness claims:

POST-MARKET EXPERIENCE 12

MEDICAL LITERATURE 8

COMPASSIONATE USE 6

EXTERNAL CONTROL ARM 6

OTHER 2

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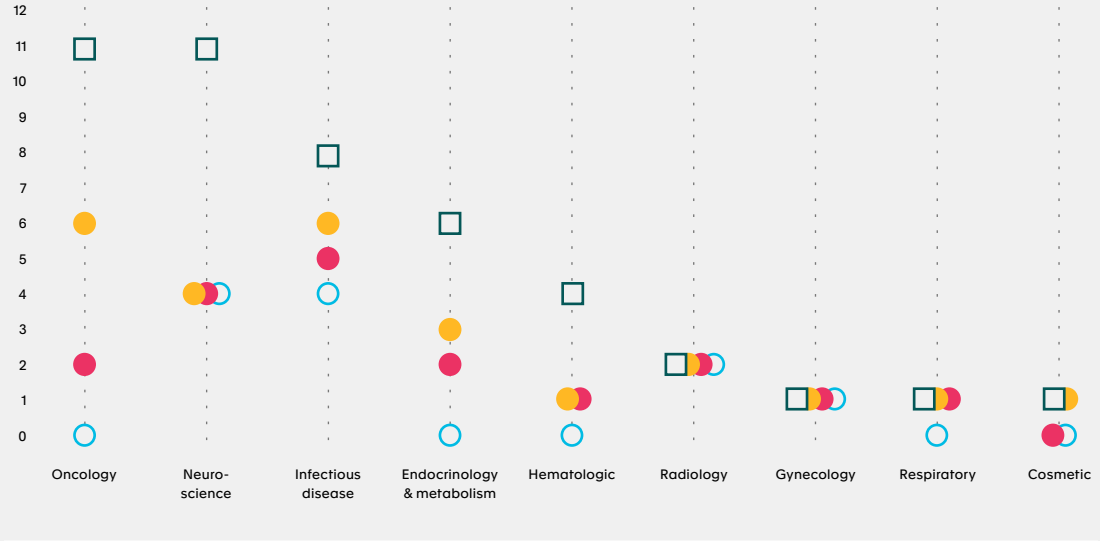
ANALYSIS ACROSS THERAPEUTIC AREAS

2019 FDA approvals that included RWE studies span nine therapeutic areas.



The following therapeutic areas (representing six approvals) did not have any RWE submissions: Dermatology, Gastrointestinal, Inflammation & Immunology, Ophthalmology.

Infectious disease

The FDA encourages sponsors to include real-world data (RWD) in submission packages when it's available. In 2019, many products for infectious diseases had been marketed outside of the U.S., so manufacturers were able to include these data, which, according to a **2005 FDA guidance**, "are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization."

Sponsors submitted RWE studies to support the approvals of the following products:

	RWE		FDA'S DECISION ON THE RWE STUDY/STUDIES			RWE	
Manufacturer/ Product	Submitted in support of	Included in FDA-defined safety population	Substantial evidence	Supportive evidence	Inconclusive	Submission type	Referenced in package insert
Sanofi **DENGVAXIA®** (Dengue Tetravalent Vaccine, Live)	Safety	●		●		Postmarketing data	●
Novartis **EGATEN™** (triclabendazole)	Safety	●		●		Compassionate use Postmarketing data	●
Shionogi **FETROJA®** (cefiderocol)	Safety				●	Compassionate use	
Bavarian Nordic. **JYNNEOS™** (Smallpox and Monkeypox Vaccine, Live, Non-Replicating)	Safety			●		Postmarketing data	
Global Alliance for TB Drug Development **PRETOMANID**	Effectiveness		●			External control arm Literature	●
Merck & Co. **PRECARBRIO™** (imipenem, cilastatin, and relebactam)	Safety			●		Postmarketing data	●

Oncology

While more than half of oncology approvals in 2019 included an RWE study, the RWE only provided supportive evidence in two of the submissions. Integrated planning with RWE studies and clinical trials is critical to ensure the RWE supports regulatory approval.

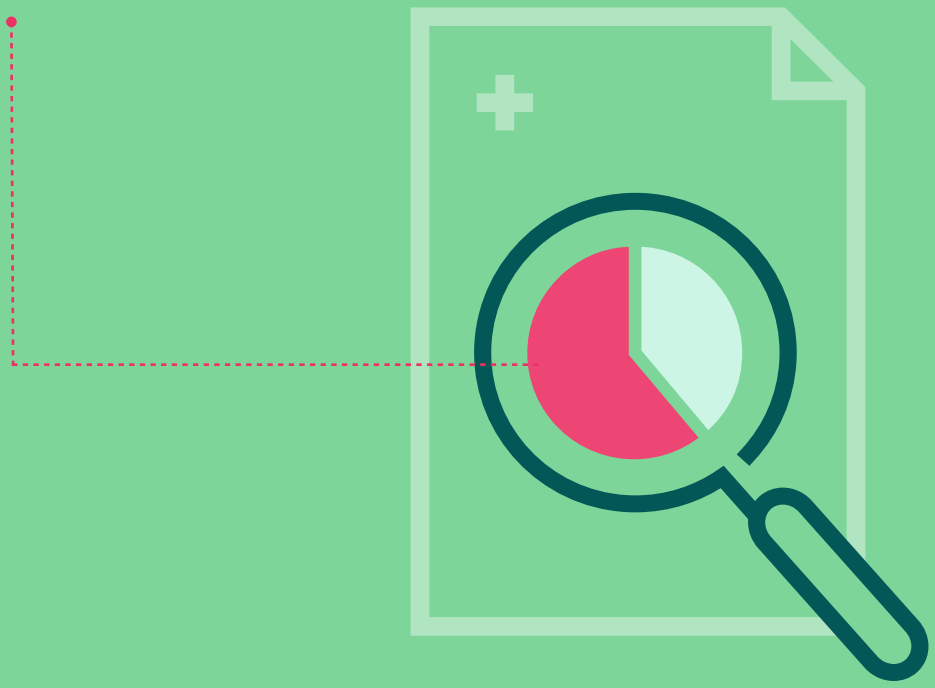
Sponsors submitted RWE studies to support the approvals of the following products:

	RWE		FDA'S DECISION ON THE RWE STUDY/STUDIES			RWE	
Manufacturer/ Product	Submitted in support of	Included in FDA-defined safety population	Substantial evidence	Supportive evidence	Inconclusive	Submission type	Referenced in package insert
Janssen **BALVERSA™** (erdafitinib)	Effectiveness				●	Standard of care external control arm	
Daiichi Sankyo **ENHERTU®** (fam-trastuzumab deruxtecan-nxki)	Effectiveness				●	Natural history external control arm	
Astellas Pharma **PADCEV™** (enfortumab vedotin-ejfv)	Safety			●		Postmarket experience	
Genentech **POLIVY™** (polatuzumab vedotin-piiq)	Effectiveness			●		Medical literature	
Genentech **ROZLYTREK®** (entrectinib)	Effectiveness				●	Standard of care external control arm	
Karyopharm Therapeutics **XPOVIO®** (selinexor)	Effectiveness				●	Natural history external control arm	

03

HOW RWE STUDIES INFORM PRESCRIBING

61 percent of decisions' subsequent package inserts refer to the RWE studies and findings.[4]



It's now routine to see RWE studies and findings cited in the package inserts of FDA-approved drugs and biologics.

See how the FDA referenced an RWE study in the package insert for **ZOLGENSMA®** (onasemnogene abeparvovec-xioi).

On May 24, 2019, the FDA approved AveXis's ZOLGENSMA "for the treatment of pediatric patients less than two years of age with a specific type of spinal muscular atrophy (SMA)." The sponsor included an expanded access study in its submission package.

This RWE study and its findings were referenced alongside clinical trial results in ZOLGENSMA's full prescribing information.

Excerpt from the package insert referring to the RWE study:

"Comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile-onset SMA provides primary evidence of the effectiveness of ZOLGENSMA."

04

DEEP DIVE: KEY COMPONENTS OF A SUCCESSFUL EXTERNAL CONTROL ARM

Pretomanid for treatment of XDR and MDR tuberculosis

External control arms (ECAs) generated from RWD can serve as viable controls for single-arm trials when conducted at the highest levels of scientific rigor.

In the case of TB Alliance's pretomanid, an ECA provided substantial evidence of effectiveness by comparing a phase 3 clinical trial to historical controls. The FDA approved pretomanid on August 14, 2019, as part of a combination regimen for the treatment of pulmonary extensively drug-resistant (XDR), treatment-intolerant or non-responsive multidrug-resistant (TI/NR MDR) tuberculosis (TB).

> "In a single phase 3 clinical trial in patients with XDR-TB or TI/NR MDR-TB, superiority of the [combination] regimen on clinical outcomes was demonstrated compared to historical controls."
>
> **FDA'S MULTI-DISCIPLINE REVIEW**

Intent of the RWE study

The study aimed to achieve a relative measurement in effectiveness outcomes between the phase 3 Nix-TB trial and historical controls.

Outcome of the RWE study

The ECA submission provided substantial evidence of effectiveness to support the approval of pretomanid. After individual matching, treatment success occurred in 89 percent of patients evaluated six months after the end of therapy—significantly exceeding the 50 percent among prespecified historical controls.

As a result, pretomanid became the second drug approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs, and TB Alliance was granted Priority Review, Orphan Drug designation, and Qualified Infectious Disease Product Designation. TB Alliance was also awarded a Tropical Disease Priority Review Voucher, which can be used to obtain a priority review designation for a future application.

A note on the literature review

TB Alliance also performed a literature review to develop the ECA and support the efficacy outcomes of the Nix-TB trial. It identified 18 eligible studies, 16 of which had results available, and found a 28 percent success rate for the historical treatment. Limitations of the literature review included the heterogeneity of the studies and outcomes, geographic and temporal differences from Nix-TB, and the possible selection of patients who would have been ineligible or not enrolled in Nix-TB.

5 REASONS why pretomanid represented a good opportunity for the use of an ECA

1

Well-defined natural history
TB is a well understood infectious disease.

2

Objective endpoint
The criteria that made up the "favorable outcome" endpoint—absence of bacteriologic failure, relapse, or clinical failure—are all objectively verifiable.

3

Patient comparability
Patient comparability was expected to be good, as the external control group was drawn from the highest-enrolling site in the clinical trial.

4

Good covariate measurement
The covariate measurement was expected to be sufficient, though subject to certain limitations. This is in line with the **FDA guidance** that "externally controlled trials are most likely to be persuasive… when the covariates influencing the outcome of the disease are well characterized."

5

Larger effect size
A larger effect size makes for a more convincing difference between groups. There were favorable outcomes at two years: The treatment effect was 84 percent, versus 11 percent in the historical controls.

Challenges acknowledged

While the ECA provided substantial evidence of effectiveness, the FDA acknowledged challenges in the Multi-Discipline Review: "Although there remains the possibility that non-randomized comparisons could be confounded, historical controls can provide convincing evidence of efficacy when the outcomes with currently available treatment options are poor and the treatment effect is too large to be easily explained by confounding factors, and this is the most straightforward interpretation of [the clinical trial] results."

In addition:

ECA patients were all newly diagnosed, while the experimental arm included prior treatment failures.

There was some imbalance at baseline, which was improved with propensity score matching.

The experimental arm followed patients for less time than the ECA.

The applicant did not submit the patient-level data for the matched historical control group, which limited reproducibility and in-depth comparison.

Learn more about how the RWE study for pretomanid was designed and executed.

05

DEEP DIVE: TAKEAWAYS FROM AN EXTERNAL CONTROL ARM WITH STUDY DESIGN LIMITATIONS

XPOVIO® (selinexor) for treatment of relapsed or refractory multiple myeloma

There is much to learn from applications with an RWE study that the FDA deemed inconclusive, and from the reasoning behind the determination.

With knowledge of the factors that may contribute to such decisions, sponsors can design RWE studies that more closely align with the FDA's evidentiary requirements, and avoid known pitfalls that may result in an application being rejected.

The application for XPOVIO (selinexor), for use in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) who have received four or more prior therapies, was submitted with an ECA as part of the evidence package. While XPOVIO was approved on July 3, 2019, the ECA did not meet the FDA's statutory evidence requirement.

> "The evidence generated from the RWD analysis is not adequate to provide context or comparison for the overall survival observed in the [clinical trial] patients [due to] the lack of comparability between the [clinical trial] and [real world] treatment groups."
>
> **FDA'S MULTI-DISCIPLINE REVIEW**

Intent of the RWE study

The goal of the ECA was to provide an estimate of the overall survival (OS) that would have been observed in the clinical trial population had patients been treated with standard of care instead of selinexor. This estimate was then used as a comparator to estimate the efficacy of selinexor on OS. The experimental arm, sourced from the STORM clinical trial, included patients with MM treated with at least three anti-MM therapies, including selinexor. The ECA used the Flatiron Health Analytic Database (FHAD) to source patients with MM and prior treatment who were treated according to standard of care.

Outcome of the RWE study

The sponsor found a median OS of 3.7 months within the RWD study, compared to 9.5 months in the STORM trial. The FDA determined that, due to methodological limitations, the RWD analysis was not an adequate comparator to the clinical trial. As a result, the FDA's label for XPOVIO does not include OS as an outcome, and only references improvements in overall response rate.

According to the FDA, limitations of the ECA included:

Major differences in selection criteria

The inclusion and exclusion criteria for the study led the STORM clinical trial cohort to have a longer expected OS when compared to the RWD population. For example, patients with a life expectancy of less than four months were excluded from the STORM trial, but not from the ECA.

Inconsistent index date

The sponsor defined the index date—the date on which follow-up for the study outcomes began, and relative to which OS is measured—for both the ECA and clinical trial cohorts as the date upon which a patient failed their previous treatment(s). But this definition was inconsistently translated across the two cohorts. Patients in the experimental arm were required to be treated with selinexor after their index date, meaning that, by definition, they survived until they received the treatment. Patients in the ECA were not required to be treated after their index date. This led to **immortal time bias**, and the FDA pointed out that "from the survival plot, the first outcome/censoring event in the [clinical] trial appears to be at approximately 1.2 months. At this time, approximately 22 percent of the FHAD patients had died or been censored."

Comparability issues

Other comparability issues contributed to differences in OS, including imbalances between trial and ECA patients that weren't adequately accounted for in the design or analysis. The clinical trial population includes patients sufficiently healthy to enroll in a clinical trial and initiate a new treatment. In contrast, a large proportion of the ECA patients did not receive additional therapy—patients who fail their current treatment but do not receive another treatment are likely to have a disease and health status that predicts a lower OS. There was also a significant imbalance in key baseline characteristics, and a high percentage of missing values for key characteristics such as staging and ECOG performance status in the RWD. Investigators used propensity score weighting to try to address covariate imbalance, but issues with sample size, missing values, and omitted covariates precluded proper covariate assessment and balancing.

Additional design issues

The FDA also identified post-hoc analysis and limited statistical power as additional limitations of the ECA.

How could the study have been considered substantial evidence?

This study highlights the importance of proactively applying principled database epidemiology in study design and planning to avoid the pitfalls mentioned previously. There are several steps the sponsor could have taken to rectify these design issues, including:

Integrated planning
Design the experimental study and the ECA together, from the beginning.

Trial sites and data
Work with trial sites to explore external control availability, calibrate data, and build evidence to meet success criteria.

Eligibility criteria
Apply the same selection criteria to both the experimental and external control arms. Creating an ECA that is a true counterfactual to the clinical trial is the only way to establish causality. For instance, in the XPOVIO example, the FDA requested that the sponsor harmonize the index dates between the clinical trial and RWD cohorts to help address immortal time bias.

Early and frequent regulator engagement
Meet proactively with the FDA to align on study design.

> "Some approaches to design and conduct of externally controlled trials could lead them to be more persuasive and potentially less biased."
>
> **THE FDA IN GUIDANCE TO INDUSTRY**

Common methodological issues with ECAs[5]

"Due to **major methodological issues** (including immortal time bias, selection bias, misclassification, confounding, and missing data), FDA did not consider RWD adequate to support regulatory decision making."

FDA'S MULTI-DISCIPLINE REVIEW

"Examination of baseline characteristics demonstrates that the RWD arm is **not sufficiently comparable** to the … clinical trial population."

FDA'S OTHER REVIEW(S)

	XPOVIO (selinexor)	BALVERSA™ (erdafitinib)	ROZLYTREK® (entrectinib)
Confounding bias	●	●	●
Selection bias	●	●	●
Post-hoc analysis	●		●
Limited cohort size (leading to lack of statistical power)	●		●
Data missingness	●	●	
Immortal time bias	●		
Lack of transparency (misclassification of treatment definitions)		●	

"Review of the presented RWD was inconclusive in establishing this class of patients as having a different expected response to these agents due to **issues with methodology**."

FDA'S MULTI-DISCIPLINE REVIEW

06

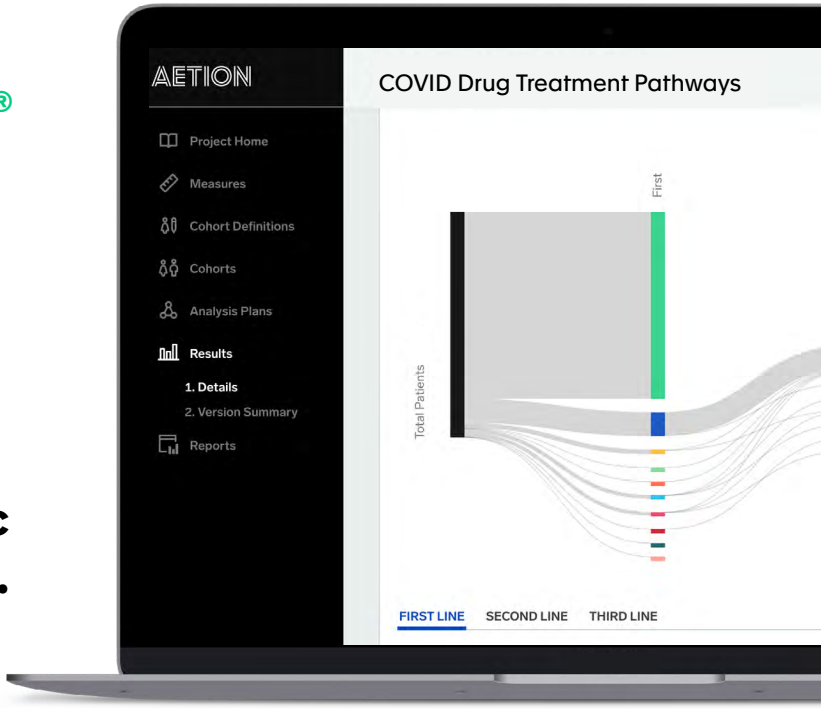
ADVANCE REGULATORY SUBMISSIONS WITH AETION

"The most intriguing part of the Aetion story is the ability to have a very consistent analytic approach that can be applied across multiple datasets."

DR. AMY ABERNETHY, on FDA's selection of Aetion

Principal Deputy Commissioner, FDA
May 2020 interview with STAT

Use Aetion Evidence Platform® (AEP) to generate decision-ready evidence at scale for regulatory, policy, and pricing decisions—anywhere scientific rigor matters most.



Rapid, reliable answers that reviewers trust

Conduct regulatory-grade studies with speed, while maintaining the highest level of scientific accuracy. AEP enables stakeholder alignment by providing transparent reporting, audit trails, and the ability for reviewers to rerun analyses.

Standard-setting partner

Aetion partners with the FDA, ICER, and ex-U.S. regulators on initiatives that set standards and build confidence in the use of RWE. For example, the FDA selected Aetion for a **research collaboration** to advance the understanding of COVID-19. We also serve as a partner on the **RCT DUPLICATE** demonstration project.

Data fluent and independent

AEP can ingest any data from any source, in native or common data model formats. Our data scientists and epidemiologists help identify the RWD sources best suited for your study. The platform provides over 1,000 pre-built, customizable clinical definitions ("measures") that allow users to work with any data source in a traceable, reproducible way.

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Work with Aetion on an RWE strategy for your next regulatory submission.

Learn more at aetion.com or contact sales@aetion.com to see the platform in action.

AETION®

Aetion is a health care analytics company that delivers RWE for the manufacturers, purchasers, and regulators of medical technologies. AEP analyzes data from the real world to produce transparent, rapid, and scientifically validated answers on safety, effectiveness, and value, across the product life cycle. Founded by Harvard Medical School faculty members with decades of experience in epidemiology and health outcomes research, Aetion informs health care's most critical decisions—what works best, for whom, and when—to guide product development, commercialization, and payment innovation into health care's modern era.

Aetion is based in New York City, and backed by investors including New Enterprise Associates (NEA), Flare Capital Partners, Lakestar, Greenspring Associates, Town Hall Ventures, McKesson Ventures, Sanofi Ventures, EDBI, Amgen Ventures, Johnson & Johnson Innovation—JJDC, Inc., UCB, and Horizon Health Services, Inc. Learn more at **aetion.com** and follow us at **@aetioninc**.

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Endnotes

1. Of the 72 FDA-approved NDAs and BLAs in 2019, we analyzed 51; we excluded the 21 assays, blood grouping reagents, and solutions. Our analysis of 2020 FDA submissions includes the 36 NDAs and BLAs approved through August 26, 2020. Note that applications that are not approved by the FDA are not available for public consumption.

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2. Substantial evidence: **According to the FDA**, "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

   Supportive evidence: A manufacturer submitted RWE studies that don't serve as the primary basis for the FDA's approval decision, but that pertain to the safety or effectiveness of a drug or biologic.

   Inconclusive: A manufacturer included an RWE study to establish or support product safety and/or effectiveness, but the FDA could not conclude as such. The RWE study does not inform the agency's decision-making.

   Not addressed: A manufacturer included an RWE study to support product safety and/or effectiveness, but the FDA did not speak to the study and/or there is no evidence that the study informed the agency's decision-making.

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3. External control arm: **According to the FDA**, "an externally controlled trial compares a group of subjects receiving the test treatment with a group of patients external to the study, rather than to an internal control group consisting of patients from the same population assigned to a different treatment."

   Medical literature: Applicants will submit previously published RWE studies to support various aspects of an approval package, including providing additional information on background rates of safety or informing a Risk Evaluation and Mitigation Strategy (REMS) plan.

   Post-market experience: This type of RWE draws from post-market data (such as outcomes and adverse effects), and it is typically submitted in support of safety claims.

   Compassionate use: Also known as expanded access programs, compassionate use programs are sources of data from which RWE is generated. Expanded access programs allow seriously ill patients to receive investigational medical products when they cannot enroll in clinical trials, and there are no comparable or satisfactory alternative therapies available.

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4. Applications containing RWE studies that are considered substantial or supportive evidence of product safety and/or effectiveness feature the RWE studies or findings in the package insert 61 percent of the time; this reflects 11 of 18 applications.

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5. Oztop I, et al. **Review Of Oncology Real-world Comparator Arm Submissions In Support Of Effectiveness Claims In 2019 FDA Original Approvals Reveals Label-grade Real-world Study Best Practices**. 2020 ICPE All Access On Demand.

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