eBook

The Role of Real-World Evidence in FDA Approvals

2021 UPDATE

AETION®

DID YOU KNOW?

78%

of FDA-approved NDAs and BLAs in 2020 included an RWE study to provide evidence of safety and/or effectiveness.

As industry prepares for additional guidance from FDA on the use of real-world evidence (RWE), Aetion conducted a systematic review of FDA approval documents to understand the role RWE can play to inform regulatory decisions.

This 2021 update of our eBook will guide you through when, where, and how RWE studies influenced the 2020 approvals of New Drug Applications (NDAs) and Biologics License Applications (BLAs).

Global biopharma organizations, leading payers, and regulatory and health technology assessment bodies use Aetion Evidence Platform® to generate decision-grade RWE. Read on to learn how Aetion can help you advance your RWE strategy.

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HOW RWE STUDIES ARE USED IN FDA APPROVALS

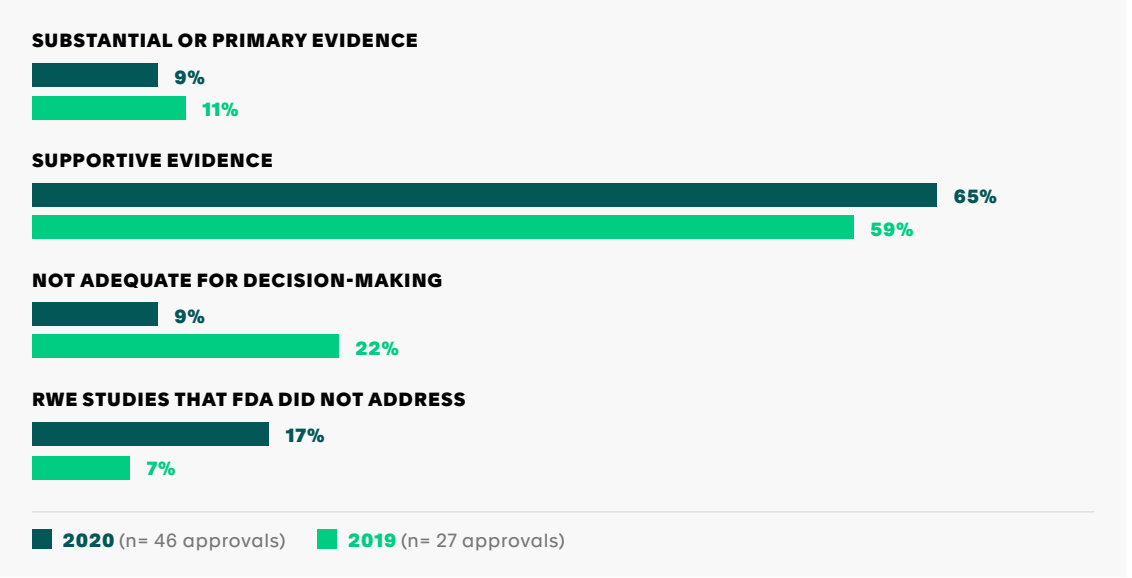
In 2019, 53 percent of FDA-approved NDAs and BLAs included an RWE study to provide evidence of safety and/or effectiveness. In 2020, that figure jumped to 78 percent.[1]

In 74 percent of the approvals that included an RWE study in 2020, the RWE influenced FDA's approval decision.

From 2019 to 2020, the use of RWE in submission packages to FDA increased substantially, and RWE continues to provide evidence of safety and/or effectiveness in a growing number of regulatory decisions.

The overall increase in RWE studies submitted to FDA may help inform future RWE guidance

How RWE studies informed FDA decisions[2]



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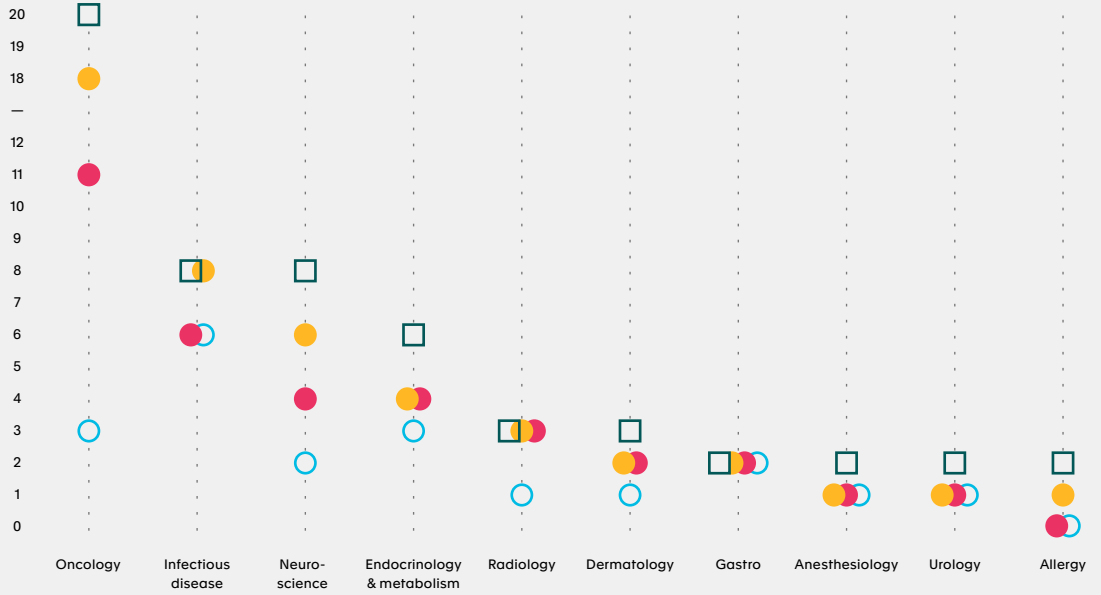
ANALYSIS ACROSS THERAPEUTIC AREAS

2020 FDA approvals that included RWE studies span 10 therapeutic areas.



Ophthalmology (representing 3 approvals) did not have any RWE submissions.

Infectious disease

In 2020, all eight approvals in infectious disease included an RWE study in the approval documents, and six of them provided substantial, primary, or supportive evidence. Additionally, six of the RWE studies submitted were mentioned in the product label.

Products approved to treat infectious diseases are often first approved in other markets where there's a greater disease burden. This may contribute to the notable use of RWE in approvals, as applicants can use data generated from the real-world usage of these interventions to generate RWE that supports new product approvals.

We share a closer look into a selection of the RWE-supported approvals for infectious disease interventions:

	RWE		FDA'S DECISION ON THE RWE STUDY/STUDIES			RWE
Manufacturer/ Product	Submitted in support of	Included in FDA-defined safety population	Substantial or primary evidence	Supportive evidence	Not adequate for decision-making	Referenced in product label
Amivas **ARTESUNATE** (for injection)	Safety & Effectiveness	●		●		●
				●		●
Bayer **LAMPIT®** (nifurtimox)	Safety & Effectiveness			●		●
				●		
Gilead Sciences **VEKLURY®** (remdesivir)	Safety & Effectiveness	●		●		●
					●	●

Oncology

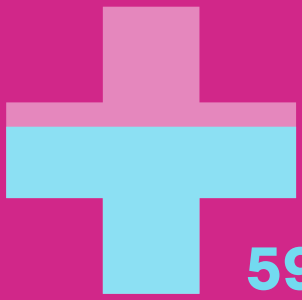
Of the 20 oncology approvals in 2020, 18 included an RWE study. Of those, 61 percent of the studies provided substantial or supportive evidence—a sizable increase from 2019, where just 25 percent of submitted RWE studies supported the product's approval.

We share a closer look into a selection of the RWE-supported oncology approvals:

	RWE		FDA'S DECISION ON THE RWE STUDY/STUDIES			RWE
Manufacturer/ Product	Submitted in support of	Included in FDA-defined safety population	Substantial or primary evidence	Supportive evidence	Not adequate for decision-making	Referenced in product label
GlaxoSmithKline **BLENREP** (belantamab mafodotin-blmf)	Effectiveness		●			
MorphoSys US Inc. **MONJUVI®** (tafasitamab-cxix)	Safety			●		
Epizyme **TAZVERIK®** (tazemetostat)	Safety & Effectiveness				●	

03

HOW RWE STUDIES INFORM PRESCRIBING



59 percent of decisions' subsequent product labels refer to RWE studies and their findings.[3]

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

See how FDA referenced an RWE study in the product label for **VEKLURY® (remdesivir)**.

On October 22, 2020, FDA approved Gilead Sciences's VEKLURY, a treatment for COVID-19 in hospitalized patients 12 years of age and older. In addition to the clinical trial evidence that provided substantial evidence of efficacy, the applicant also included emergency use authorization (EUA) data, compassionate use program data, and four additional studies to provide additional evidence of safety and efficacy.

FDA referenced RWE studies and findings from the EUA and compassionate use program data alongside clinical trial results in VEKLURY's full prescribing information.

Excerpt from the EUA Fact Sheet for Healthcare Providers referring to the RWE studies:

"The safety of VEKLURY is based on data from three Phase 3 studies in 1,313 hospitalized adult subjects with COVID-19, from four Phase 1 studies in 131 healthy adults, and from patients with COVID-19 who received VEKLURY under the Emergency Use Authorization or in a compassionate use program."

04

DEEP DIVE: KEY COMPONENTS OF A SUCCESSFUL EXTERNAL CONTROL ARM

EVRYSDI™ (risdiplam) for spinal muscular atrophy

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 Genentech's EVRYSDI (risdiplam), an ECA composed of several natural history studies provided substantial evidence of effectiveness.[4] FDA approved EVRYSDI on August 7, 2020, to treat spinal muscular atrophy (SMA) in infants two months of age and older.

Intent of the RWE study

The applicant referenced multiple published natural history studies as a benchmark for comparison to the **FIREFISH trial**, a phase 2/3 open-label, single-arm trial. The primary objective of these studies was to demonstrate that patients with Type 1 SMA are never able to sit without support. The secondary objective was to show the rates of survival and ventilator-free survival. The applicant also referenced natural history studies as context for baseline scores of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, known as CHOP-INTEND score. CHOP-INTEND uses a zero-to-64-point scoring scale, in which higher scores indicate better motor function.

Protocols for RWE generation

While FDA at first expressed preference for a placebo control for FIREFISH—citing concerns around bias and differences in study populations in the RWE arm—it eventually agreed to the single-arm trial, with conditions. To demonstrate efficacy, the single-arm trial had to show that at least five out of 40 patients could sit without support, and the applicant had to "provide data that supports the assertion that untreated children essentially never would be expected to reach this milestone as defined by the protocol."

To construct the ECA, the applicant relied on several natural history studies to serve as contextual controls for the primary and secondary endpoints, as well as to inform the CHOP-INTEND baseline score.

Protocols for RWE generation continued

To support the primary endpoint and demonstrate that patients with Type 1 SMA are never able to sit without support, the applicant submitted five studies: **Finkel et al.** 2014a; **Finkel et al.** 2015; **Faravelli et al.** 2015; **De Sanctis et al.** 2016; and **Kolb et al.** 2017.

For the secondary endpoints of survival and ventilation-free survival, the applicant submitted an additional five studies: **Finkel et al.** 2014b, Kolb et al. 2017, **Oskoui et al.** 2007, **Rudnik-Schöeneborn et al.** 2009, and and **CARNIVAL Type 1**, a phase 1/2 study.

To provide context for the trial participants' CHOP-INTEND baseline scores, the applicant submitted four studies: **Darras** 2016; De Sanctis et al. 2016; **De Sanctis et al.** 2017, and Kolb et al. 2017.

Outcome of the RWE study

The RWE studies provided substantial evidence of effectiveness to support the approval of EVRYSDI. FDA stated that the natural history ECA "showed improvements in multiple clinical functional measures compared to the natural history of SMA, including motor function and developmental milestones as well as survival and ventilation-free survival."

When discussing the primary endpoint of the FIREFISH experimental arm compared to the natural history studies, FDA's biometrics review concluded "the evidence from FIREFISH ... is not well controlled." However, the clinical reviewer came to a different conclusion, stating it "considers the external natural history control as sufficient to describe the FIREFISH study as 'well-controlled' because no Type 1 SMA patients would be expected to achieve sitting without support in the natural history of the disease." FDA also noted that the threshold of five patients sitting without support was previously agreed upon by FDA and the applicant before the study initiation, and stated that such an endpoint was "well-defined with a low potential for bias."

For the secondary endpoint of ventilation-free survival, 94 percent of the higher dose cohort in FIREFISH was alive after 12 months. FDA concluded that "the FIREFISH Part 1 study result indicates reduced mortality and permanent ventilation in the risdiplam group compared to the natural history of Type 1 SMA."

This study also showed a four point increase in CHOP-INTEND score in 88 percent of the higher dose cohort—an improvement in motor function never before seen in two of the natural history studies. 53 percent of the participants in this cohort also-achieved head control, compared to 39 percent achieving partial head control in the De Sanctis study.

> "Further evidence of the benefit of risdiplam in treating infants with Type 1 SMA was provided by an open-label, historically controlled, multicenter study that showed improvements in multiple clinical functional measures compared to the natural history of SMA. This study provides evidence of reduced mortality and permanent ventilation in the risdiplam group compared to the natural history of Type 1 SMA."
>
> **FDA'S CLINICAL REVIEW**

5 REASONS why risdiplam represents a good opportunity for the use of an ECA

1

Well-defined natural history
The natural progression of SMA is well understood.

2

Objective endpoint
The criteria that made up the "favorable outcome" endpoint—sitting without support and ventilation-free survival—are both objectively verifiable endpoints, though they may not be evident in traditionally structured data sources.

3

Patient comparability
While there has been some therapeutic innovation in the past few years, historical data are expected to be of good quality. Historic subtype classification may be problematic.

4

Good covariate measurement
The covariate measurement was expected to be sufficient, though subject to certain limitations.

5

Larger effect size
Since no patients with SMA would be able to sit without support, it is clear that the effect size is large and easily measurable.

05

LEARNINGS FROM EXTERNAL CONTROL ARMS WITH STUDY DESIGN LIMITATIONS

There is much to learn from applications with an RWE study that FDA deemed not adequate for decision-making, and from the reasoning behind the determination.

By understanding the reasoning behind FDA's decision, applicants can design RWE studies that more closely align with evidentiary requirements. This can also help them avoid common pitfalls that may result in an RWE study being rejected or not considered as part of FDA's decision.

Common methodological issues with ECAs[5,6]

"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

	XPOVIO® (selinexor)	BALVERSA™ (erdafitinib)	ROZLYTREK® (entrectinib)	TAZVERIK™ (tazemetostat)
Confounding bias	●	●	●	●
Selection bias	●	●	●	●
Post-hoc analysis	●		●	
Limited cohort size	●		●	
Data missingness	●	●		●
Immortal time bias	●			
Lack of transparency		●		●

"The protocol for the natural history study **does not provide adequate detail** regarding quality of data, validity of endpoint assessments, and design choices, rendering the results of the study uninterpretable."

FDA'S ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

How can you design ECAs that support regulatory decision-making?

There are several actions applicants can take to rectify common missteps in RWE studies, 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.

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

Target trial emulation
Think of the RWD study as a randomized controlled trial, and mimic aspects of the **"target trial"** across the design, protocol, and analysis phases to ensure confounding control.

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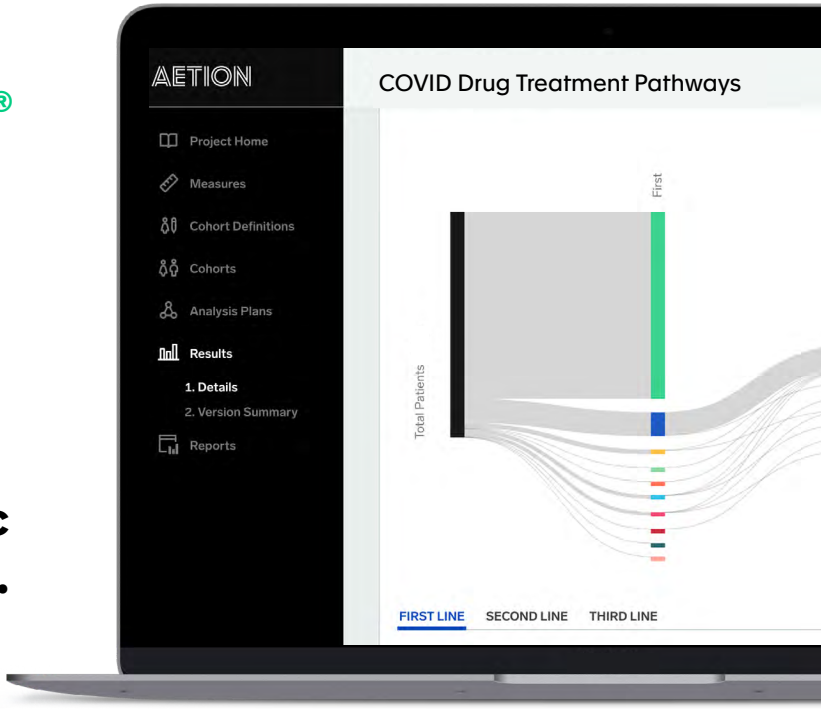
GENERATE DECISION-GRADE RWE WITH AETION

"Aetion Evidence Platform has been tremendous for us with regards to delivering RWE more efficiently. From an operational perspective, it has helped us generate high quality evidence faster, and allows us to deliver more for our stakeholders."

DR. BOB LOCASALE
Head of RWE, Sanofi

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 FDA, ICER, NICE, and other global regulators and health technology assessment bodies on initiatives that set standards and build confidence in the use of RWE. For example, 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 1,500 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 to advance your RWE strategy.

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AETION®

Aetion delivers real-world evidence for the manufacturers, purchasers, and regulators of medical treatments and technologies. The Aetion Evidence Platform® analyzes data from the real world to produce transparent, rapid, and scientifically validated answers on safety, effectiveness, and value. 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.

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

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Endnotes

1. Of the 161 FDA-approved NDAs and BLAs in 2019, we analyzed 51. Of the 147 FDA-approved NDAs and BLAs in 2020, we analyzed 59. Our analyses included approvals defined by **FDA's classification guide** as NDA Type 1 (New Molecular Entities, or NMEs) and Type 9 ("new indication or claim, drug not to be marketed under Type 9 NDA after approval"), as these are the core mechanisms for FDA to consider marketing authorization for new molecules. We excluded the remainder of FDA's NDA classifications, meaning non-NME approvals, assays, blood grouping reagents, and solutions. Note that applications that are not approved by FDA are not available for public consumption, and therefore not reflected in our analysis.

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2. **Substantial or primary evidence:** Evidence which makes the primary case for product safety and/or effectiveness is referred to as "substantial evidence" by FDA's Center for Drug Evaluation and Research, and as "primary evidence" by FDA's Center for Biologics Evaluation and Research. **According to 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 FDA's approval decision, but that pertain to the safety or effectiveness of a drug or biologic.

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

   RWE studies that FDA did not address: A manufacturer included an RWE study to support product safety and/or effectiveness, but 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. 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 product label 59 percent of the time; this reflects 20 out of 34 applications.

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4. Honig N, Louder A. "**CDER-Approved NDA for EVRYSDI™ (risdiplam)**," *FDA Decision Alerts*, Aetion, December 17, 2020.

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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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6. Purpura C, Patrick A. "**CDER-Approved NDA for TAZVERIK™ (tazemetostat)**," *FDA Decision Alerts*, Aetion, August 14, 2020.

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Updated as of October 2021.