



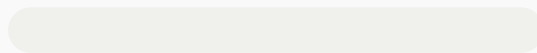
VOLUME #3

# How Real-World Evidence is Impacting Regulatory Decision Making

A collection of 10 recent regulatory decisions based on RWE

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## The Continued Growth of Real-World Evidence (RWE) Influence

In [Volumes 1](#) and [2](#) of *How Real-World Evidence is Impacting Regulatory Decision Making*, we provided examples of the growing use of RWE when regulatory agencies are making decisions on drug submissions. The use of RWE continues to grow and is becoming a standard for helping to prove the safety and/or efficacy of drugs submitted for approval.

In December 2022, the FDA announced a new funding opportunity for projects to further promote the possible use of real-world data (RWD) to generate RWE related to drug development. The goal of the program is to incentivize more projects that close the knowledge gaps on the use of RWD and RWE for regulatory submissions.<sup>1</sup>

A recent survey revealed that 90% of life sciences organizations have either established or are currently investing in increasing RWE capacity for use in their research activities.<sup>2</sup> As a result, the global RWE solutions market is predicted to reach \$78.80 billion by 2030, growing by an expected 8.1% each year. Drivers of this growth include government regulatory support and a transition from volume to value-based care. The increase in chronic diseases is also a driver of the RWE market growth.<sup>3</sup>

RWE is not only being used by the FDA. The use of RWE is also gaining momentum in the regulatory decisions of the European Medicines Agency (EMA). A study of RWE use by the FDA from 2019-2021 found that out of 136 approvals, 116 (85%) included RWE. The number of approvals that include an RWE study increased from 75% in 2019 to 90% in 2020 to 96% in the first half of 2021. For the EMA Market Authorization Applications (MAAs) from 2018 to 2019, 39% included RWE. For EMA Extension of Indication (EOIs), 18.3% contained RWE.<sup>4</sup>



# REAL-WORLD EVIDENCE TIMELINE

SEPTEMBER  
**2007**

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) defines real-world evidence as “data from retrospective or prospective observational studies and observational registries and provides insights beyond those addressed by randomized controlled trials.”<sup>5</sup>

MAY  
**2008**

FDA launches Sentinel Program to monitor post approval safety of drugs, vaccines, and medical devices through a national reporting network.<sup>6</sup>

FEBRUARY  
**2014**

FDA approves Vimizin for treatment of Morquio A Syndrome using real-world data generated on studies of related diseases.<sup>7</sup>

FEBRUARY  
**2015**

FDA approves Ibrance for postmenopausal women with advance breast cancer based on clinical real-world data showing the drug is likely to have a positive clinical effect on patients.<sup>8</sup>

DECEMBER  
**2016**

U.S. Congress passes the 21st Century Cures Act mandating the evaluation of real-world evidence in regulatory decision making.<sup>9</sup>

APRIL  
**2017**

FDA approves Brineura as a treatment for a specific form of Batten disease using a single arm clinical study and a comparator arm from a natural history cohort.<sup>10</sup>

JUNE  
**2017**

FDA approves a new indication for a transcatheter aortic valve replacement (TAVR) without requiring any new clinical trials and instead relying on records of the product’s actual patient use.<sup>11</sup>

JUNE  
**2017**

Japan issues an approach for the use of medical information databases in post marketing pharmacovigilance.<sup>12</sup>

**2018 - 2019**

63 of 158 products submitted for marketing authorization applications (MAAs) to the European Medicines Agency (EMA) included real-world evidence.<sup>13</sup>

JANUARY JUNE  
**2019 - 2021**

116 of 136 FDA approvals (85%) included real-world evidence in some form.<sup>14</sup>



# FDA DESIGNATIONS & EXPEDITED PROGRAMS

## FDA Designations & Expedited Programs

In many cases where RWE is used to influence regulatory decision-making, the FDA will grant designations and expedited programs during the approval process. Below are the most common designations and programs.

<b>Accelerated Approval</b>	In 1992, mindful of the fact that it may take an extended period to measure a drug's intended clinical benefit, the FDA instituted the Accelerated Approval regulations. These regulations allow drugs for serious conditions filling an unmet medical need to be approved based on a surrogate endpoint – enabling the FDA to approve them faster. <sup>15</sup>
<b>Breakthrough Therapy</b>	This designation was established by the FDA in 2012 for the purpose of shortening the development and review process for drugs that have shown signs of extraordinary benefit early in the clinical development process. This designation is not considered approval and the drug must still go through the regular clinical testing and review by the FDA. <sup>16</sup>
<b>Fast Track</b>	The FDA established the Fast Track designation in 1997 when Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA). <sup>17</sup> Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier and addresses a broad range of serious conditions. <sup>18</sup>
<b>Orphan Drug</b>	This designation was established in 1983 as part of the Orphan Drug Act. It provides financial incentives to attract industry's interest through a seven-year period of market exclusivity for a drug approved to treat an orphan (rare) disease, even if it were not under patent, and tax credits of up to 50 percent for research and development expenses. <sup>19</sup>
<b>Priority Review</b>	In 1992, the FDA established this designation as a way to accelerate drug review time. The designation set a goal for the FDA to take action on an application within six months instead of the normal 10-month goal. A Priority Review designation receives direct overall attention and resources to the evaluation of drugs that, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications. <sup>20</sup>

**While it's safe to say that RWE continues to grow in acceptance, there is still uncertainty around the best way to employ it. We have curated the following 10 use cases to shed light on how RWE is moving the regulatory needle.**



## TAZVERIK

Manufacturer:

Epizyme

Approved:

January 23, 2020

## Background

Epithelioid sarcoma (ES) is a rare soft tissue sarcoma of young adults that presents as a painless, slow growing mass. Complete surgical resection can cure the disease, but it can recur and metastasize in late stages.<sup>21</sup> Epithelioid accounts for about 1% of all soft tissue sarcomas in the U.S. There are believed to be less than 1,000 people in the U.S. with the disease.<sup>22</sup> Tazverik is a type of histone methyltransferase that blocks certain enzymes involved in gene expression and cell division and may help cancer cells from growing.<sup>23</sup>

## RWE Use

The FDA evaluated efficacy through a single-arm cohort (Cohort 5) of a multi-center trial (EZH-202) in patients with histologically confirmed, metastatic or locally advanced epithelioid sarcoma. Epizyme submitted a natural history study on patients with ES who had not received Tazverik as a control arm to support full approval, specifically to determine safety and efficacy in a real-world setting.<sup>24</sup>

## Approval & Impact

Tazverik is the first FDA-approved treatment option specifically for patients with epithelioid sarcoma.<sup>25</sup> The FDA granted Accelerated Approval to Tazverik for adults and children 16 and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.<sup>26</sup> Tazverik also received Orphan Drug designation.

## ZYNYZ

Manufacturer:

Incyte

Approved:

March 22, 2023

## Background

Merkel cell carcinoma (MCC) is a rare disease in which malignant cancer cells form in the skin. Sun exposure and having a weak immune system can impact the risk of MCC.<sup>27</sup> Approximately 3,000 new cases are diagnosed each year and experts predict that this will increase to 3,250 cases annually in the U.S. by 2025.<sup>28</sup> Zynyz is a humanized monoclonal antibody that targets programmed death receptor-1 (PD-1) to treat adults with MCC.<sup>29</sup>

## RWE Use

Safety and efficacy was based on an evaluation conducted in PODIUM-201, an open-label, multi-regional, single-arm study that assessed 65 patients with metastatic or recurrent locally advanced MCC who hadn't yet been treated for advanced disease. The review used the FDA's [Assessment Aid](#), a voluntary submission from participants to enable the FDA's assessment.<sup>30</sup>

## Approval & Impact

The FDA action marks the first regulatory approval for Incyte-PD-1 inhibitor based on the results of the PODIUM-201 trial. Zynyz now gives clinicians another first-line treatment option against MCC that can provide lasting impact to MCC patients which is often a difficult disease to treat.<sup>31</sup> Application for Zynyz was granted Priority Review and received Fast Track and Orphan Drug designation by the FDA.<sup>32</sup>



## BESREMI

Manufacturer:  
PharmaEssentia  
Corporation

Approved:  
November 12, 2021

## Background

Polycythemia vera (PV) is a blood disease that causes an overproduction of red blood cells. This excess thickens the blood, slows blood flow, and increases the chance of blood clots. PV, a rare disease, impacts about 6,200 people in the U.S. each year.<sup>33</sup>

Besremi is an innovative monopegylated, long-acting interferon, which shows its effects in blood cells that have PV in the bone marrow.<sup>34</sup>

## RWE Use

Safety and effectiveness of Besremi were assessed in a multi-center, single-arm trial that lasted 7.5 years. The trial followed 51 adult patients in a real-world setting with PV and effectiveness was determined by finding how many patients achieved complete hematological response. Of the patients followed, 61% achieved that threshold.<sup>35</sup>

## Approval & Impact

Besremi is the first FDA-approved drug for PV that patients can take regardless of their treatment history. It is the first interferon therapy specifically approved for PV and fits a clear unmet need. Besremi received Orphan Drug designation by the FDA.<sup>36</sup>



## ONGENTYS

Manufacturer:  
Neurocrine Biosciences

Approved:  
April 27, 2020

### Background

Parkinson's disease (PD) is a brain disorder that causes unintended or uncontrollable movements such as shaking, stiffness, and difficulty with balance and coordination.<sup>37</sup> PD is the second-most common neurodegenerative disorder in the U.S. with approximately 500,000 Americans diagnosed.<sup>38</sup> Ongentys is an oral, selective catechol-O-methyltransferase (COMT) inhibitor that helps block the COMT enzyme that breaks down levodopa, the most effective therapy for controlling motor symptoms in PD patients.<sup>39</sup>

### RWE Use

FDA approval was based on two randomized controlled trials (RCTs) and real-world post market data from 38 clinical studies that supported the safety and efficacy of Ongentys. The data came from Germany, Italy, Portugal, Spain, and the United Kingdom and included 420,167 patient-months.<sup>40</sup>

### Approval & Impact

Ongentys is the first and only approved once-daily COMT inhibitor. It decreases "off" episodes and increases "on" time without problematic impairment of voluntary movement (Dyskinesia) when combined with Levodopa/Carbidopa in PD patients. Ongentys is an important new treatment for PD patients since first-line treatments like levodopa tend to lose effectiveness over time. Studies have shown that adding Ongentys to levodopa therapy leads to more consistent motor symptom control.<sup>41</sup>

## VIMIZIM

Manufacturer:  
BioMarin

Approved:  
March 22, 2022

### Background

Mucopolysaccharidosis type 4A (MPS IV) is an autosomal recessive genetic disorder that mainly impacts the skeleton. People with MPS IV develop various skeletal abnormalities including shortness, knock knees, and abnormalities of the ribs, chest, spine, hips, and wrists. It is thought that one in 200,000 to 300,000 people suffer from MPS IV.<sup>42</sup> People born with MPS IV are missing, or lack enough of, an enzyme known as *N*-acetylgalactosamine-6-sulfatase, or GALNS, which breaks down and recycles glycosaminoglycans, or GAGs, a type of cellular waste. Vimizim can help replace the deficient GALNS to help restore some cell function.<sup>43</sup>

### RWE Use

Vimizim was originally rejected by the National Institute for Health and Care Excellence (NICE), the UK's medicine costs watchdog, in November 2021. However, following collection and review of real-world data from 69 people who received treatment since 2015, NICE decided to recommend Vimizim. The data collection enabled new RWE on the benefits of the treatment.<sup>44</sup>

Vimizim – Continued

## Approval & Impact

Vimizim was recommended by NICE for routine use for the treatment of MPS IV. It becomes the first disease modifying treatment recommended by NICE for people suffering from the rare, severely life-threatening disease. The decision is significant for MPS IV patients who are now able to access this first of its kind treatment.<sup>45</sup>

### SKYCLARYS

Manufacturer:  
Reata

Approved:  
February 28, 2023

## Background

Friedreich's ataxia (FA) is a neuromuscular disease that impacts the nervous system and the heart. FA occurs in about one in every 50,000 people globally, making it the most common in a group of related disorders called hereditary ataxias.<sup>46</sup> FA is a rare, inherited disease that is characterized by impaired coordination and walking.<sup>47</sup> Skyclarys is an oral, once-daily Nrf2 transcription factor that binds to the Kesp1 gene, restoring mitochondrial function and reducing inflammation.<sup>48</sup>

## RWE Use

The efficacy and safety to treat FA was monitored in an open label extension (OLE) study following initial assessment in a nearly yearlong randomized, placebo-controlled, double blind study. Following original analysis, patients who continued treatment with Skyclarys were followed in an OLE for up to three years. The real-world data from these individuals showed they performed better on the modified Friedreich's Ataxia Rating Scale (mFARS) than those in a matched set of untreated patients from a natural history study.<sup>49</sup> The OLE also provided the FDA with the necessary proof of safety and neurological function measures such as speaking, swallowing, and standing.<sup>50</sup>

## Approval & Impact

Skyclarys is the first ever therapy specifically indicated for the treatment of FA. It was approved under Orphan Drug, Fast Track, Priority Review, and Rare Pediatric Disease designations.<sup>51</sup> Usually the FDA only approves drugs after two clinical trials, but because of a lack of candidates for a second trial, the agency accepted real-world data collected over time from the same trial patients. This is a significant development for the treatment for diseases that impact few individuals and further demonstrates the FDA's acceptance of RWE.<sup>52</sup>



## LAMZEDE

Manufacturer:  
Chiesi Global Rare  
Diseases

Approved:  
February 16, 2023

## Background

Alpha-mannosidosis (OMIM) is an extremely rare monogenic disorder caused by alpha-mannosidase deficiency. It occurs in between one in 500,000 and 1,000,000 live births but because it is typically underdiagnosed, it is thought the incidence of it is much higher.<sup>53</sup> Lamzede acts similarly to the alpha-mannosidase enzyme in the body and restores normal cellular activity in those suffering from the disease.<sup>54</sup>

## RWE Use

Researchers used the Sparkle Registry, an alpha-mannosidosis registry, to conduct the study to provide real-world data on the long-term safety and effectiveness of Lamzede during routine clinical care.<sup>55</sup> Chiesi provided the study to the FDA in 2022 during its approval process.<sup>56</sup>

## Approval & Impact

Lamzede is the first enzyme replacement therapy approved in the U.S. for the treatment of alpha-mannosidosis.<sup>57</sup> Current treatment is mostly based on treating the symptoms of the disease where Lamzede has the potential to address its cause. The FDA accepted Priority Review for Lamzede<sup>58</sup> and gave it an Orphan Drug designation.<sup>59</sup>



## CIBINQO

Manufacturer:

Pfizer

Approved:

January 14, 2022

## Background

Atopic dermatitis, commonly known as eczema, is a non-contagious inflammatory skin condition. It is a chronic disease categorized by dry, itchy skin. Individuals with eczema are also vulnerable to bacterial, viral, and fungal skin infections. Eczema is seen in approximately 30 percent of individuals in the U.S.<sup>60</sup> Cibinqo is an oral, once daily, Janus kinase 1 inhibitor therapy for adults whose disease is not adequately controlled with other systemic drug products.<sup>61</sup>

## RWE Use

In addition to results of three Phase 3 clinical trials, safety and efficacy of Cibinqo was evaluated through a randomized dose-ranging trial and a long term, open label, extension trial (JADE EXTEND).<sup>62</sup> Real-world data was collected from more than 223 patients for 12 weeks and used to supplement the clinical trial results in Pfizer's submission to the FDA.<sup>63</sup>

## Approval & Impact

The FDA accepted Priority Review for Cibinqo and gave it a Breakthrough Therapy designation.<sup>64</sup> Cibinqo now offers relief to the millions of patients who suffer daily from a condition that can cause intense and persistent itching, pain, discomfort, and distress if left uncontrolled and are not adequately managed by current treatment.<sup>65</sup>



## RELYVRIO

Manufacturer:  
Amylyx Pharmaceuticals

Approved:  
September 29, 2022

## Background

Amyotrophic-Lateral-Sclerosis (ALS) is a rare disease that attacks and kills the nerve cells that control voluntary muscles involved in chewing, walking, breathing, and talking. About 5,000 people in the U.S. are diagnosed with ALS each year and nearly 20,000 Americans are living with the disease today.<sup>66</sup> Relyvrio is an oral, fixed-dose combination therapy that has been shown to significantly slow the loss of physical function in ALS patients.<sup>67</sup>

## RWE Use

In March 2022, an FDA advisory board voted not to approve Relyvrio saying that the data from the clinical trial did not definitively conclude the medication was effective in treating ALS. Amylyx then conducted an open-label extension (OLE) study to collect real-world data from patients who participated in the trial who continued taking the drug.

## Approval & Impact

Presented with real-world data from the OLE along with further review of the original data, the advisory board voted for approval.<sup>68</sup> The FDA granted this application Priority Review and Orphan Drug designations.<sup>69</sup> It is hoped that Relyvrio will improve the early phase of the disease and enable patients to function and communicate more independently longer. The medication becomes one of the few therapies available to treat ALS.<sup>70</sup>

**QALSODY**

Manufacturer:  
Biogen

Approved:  
April 25, 2023

## Background

SOD1-ALS is a rare neurodegenerative disorder mostly affecting upper and lower motor neurons. It leads to a progressive paresis and atrophy of skeletal muscles resulting in quadriplegia and fatal respiratory failure.<sup>71</sup> Approximately 2% of ALS cases are associated with mutations in the SOD1 gene. The FDA estimates that fewer than 500 individuals suffer from SOD1-ALS in the U.S.<sup>72</sup> Qalsody is a prescription medicine targeting the SOD1 gene that produces an enzyme called superoxide dismutase. This enzyme protects the body's cells from damaging oxidative stress.<sup>73</sup>

## RWE Use

Efficacy of Qalsody was first shown in a 28 week random, double blind, placebo-controlled study. Following the trial, Biogen conducted a 52 week open-label extension (OLE) study to gather real-world data of the drug's effectiveness. The RWD collected from the OLE showed similar effectiveness as shown in the clinical trial and supported Biogen's application when they submitted it to the FDA.<sup>74</sup>

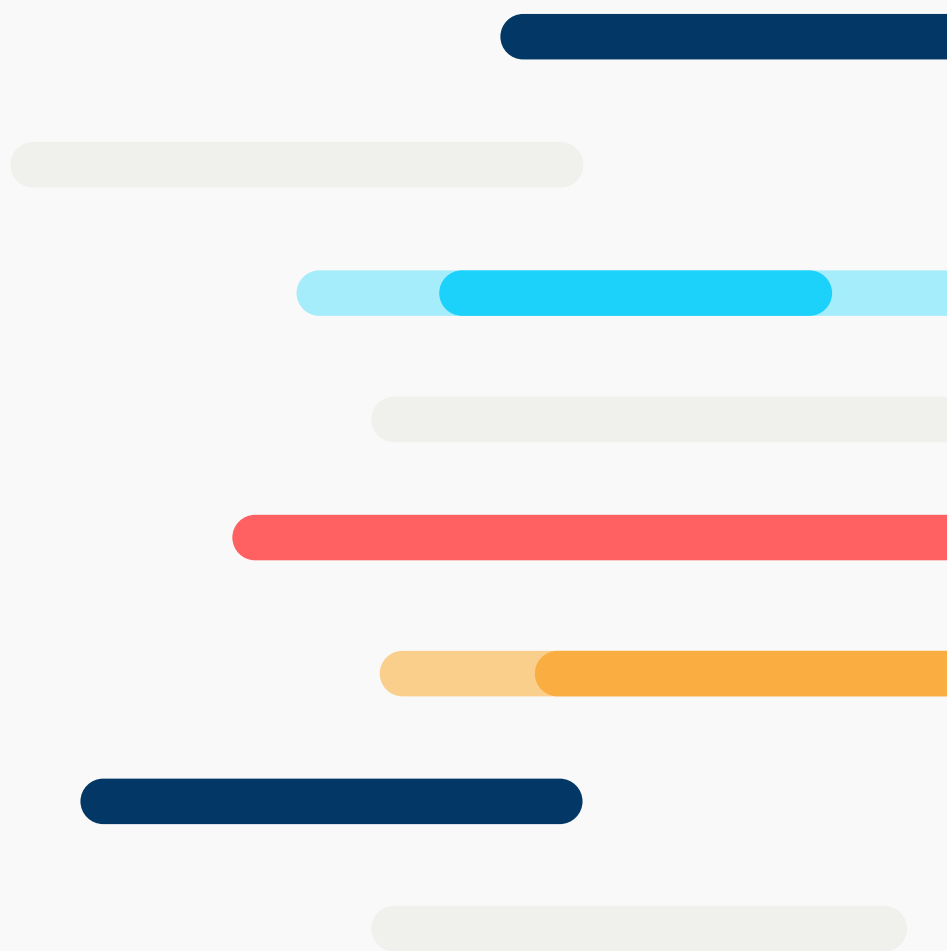
## Approval & Impact

Qalsody received Priority Review and was given Orphan Drug and Fast Track designations by the FDA.<sup>75</sup> It is the first approved treatment that targets a genetic cause of ALS and is thought to be a major scientific advancement in the treatment of ALS. The hope is that this drug can help people living with this rare version of ALS experience a reduction in decline in strength as well as clinical and respiratory function.<sup>76</sup>



# SUMMARY

The use of RWD and RWE in regulatory decision making continues to accelerate making life-saving drugs available more quickly. The growing use of open label extensions (OLE) is another way in which RWD and RWE have become significant in the decision making process. These OLEs – studies that enroll participants of a previous clinical trial – are designed to collect long term safety and effectiveness data in a real world setting. As RWD and RWE become even more readily available, reliance on them by researchers and regulatory agencies will continue to grow. These 10 examples show the increasing prominence of RWE and RWD in regulators decisions.



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- <sup>63</sup> Phase 3 efficacy and safety of abrocitinib in adults with moderate-to-severe atopic dermatitis after switching from dupilumab (JADE EXTEND). [Click Here](#).
- <sup>64</sup> New Drug Therapy Approvals 2022, [Click Here](#).
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