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VOLUME #4

How Real-World Evidence is Impacting Regulatory Decision Making

A collection of 12 recent regulatory decisions based on RWE

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INTRODUCTION

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

In Volumes 1, 2, and 3 of How Real-World Evidence is Impacting Regulatory Decision Making, we provided examples of the growing use of RWE in regulatory agency submissions. The use of RWE continues to grow and is becoming a standard for helping to prove the safety and efficacy of drugs submitted for approval.

Our first three volumes highlighted the ways in which RWE was integral in bringing important new therapies to market. First time therapies for rare diseases like Tazverik for treating patients with epithelioid sarcoma, Besremi for polycythemia vera PV that patients can take regardless of their treatment history, and Koselugo, for the treatment of Neurofibromatosis type 1, an incurable, rare and debilitating genetic condition, all included significant RWE in their applications 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.[1]

In December 2023, the FDA issued new guidance on the use of RWE to support regulatory decision-making for medical devices, expanding the use of RWD/RWE to include devices used in healthcare treatments. Evidence submitted for approval of medical devices often comes from non-clinical sources or clinical studies. With this new guidance, the FDA is recognizing that a large and important amount of RWD covering medical devices exists and is routinely collected in the course of treatment and management of patients.[2]

It is abundantly clear that going forward, RWE will continue to play an integral role in the decision-making process by regulatory bodies.

- **90% of life sciences organizations have either established or are currently investing in increasing RWE capacity for use in their research activities.**
- **The global RWE solutions market is predicted to reach $78.80 billion by 2030, growing by an expected 8.1% each year.**
- **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.**

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."[5]

MAY
2008

FDA launches Sentinel Program to monitor post approval safety of drugs, vaccines, and medical devices through a national reporting network.[6]

FEBRUARY
2014

FDA approves Vimizin for treatment of Morquio A Syndrome using real-world data generated on studies of related diseases.[7]

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.[8]

DECEMBER
2016

U.S. Congress passes the 21st Century Cures Act mandating the evaluation of real-world evidence in regulatory decision making.[9]

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.[10]

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.[11]

JUNE
2017

Japan issues an approach for the use of medical information databases in post marketing pharmacovigilance.[12]

2018 - 2019

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

JANUARY JUNE
2019 - 2021

116 of 136 FDA approvals (85%) included real-world evidence in some form.[14]

DECEMBER
2022

FDA announces a new funding opportunity for projects to further promote the use of RWD to generate RWE related to drug development.[15]

DECEMBER
2023

FDA issues new guidance on the use of RWE to support regulatory decision-making for medical devices.[16]

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.

Accelerated Approval	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.[17]
Breakthrough Therapy	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.[18]
Fast Track	The FDA established the Fast Track designation in 1997 when Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA).[19] 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.[20]
Orphan Drug	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.[21]
Priority Review	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 withing 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.[22]

IMMUNOLOGY

COSENTYX

Manufacturer:
Novartis

Approved:
October 9, 2023

Background

Psoriatic arthritis, which affects an estimated 1.5 million people in the U.S., can cause severe pain, swelling, and tenderness in joints among other symptoms.[23] In 2015, the FDA approved Cosentyx to treat plaque psoriasis. The following year, Cosentyx was approved as treatment for psoriatic arthritis and in subsequent years was approved for treatment in children and adolescents. Cosentyx is injected under the skin once a month using an automatic "pen" injector or a pre-filled syringe.[24] Novartis learned that many patients preferred IV infusion in the provider office and developed an IV formulation for the drug.

RWE Use

Cosentyx is a proven medicine that has been studied clinically for more than 14 years. FDA approval was backed by eight years of real-world evidence and five years of long term safety and efficacy in adults with moderate to severe plaque psoriasis.[25]

Approval & Impact

Cosentyx IV is the first new intravenous treatment option in six years for adults with psoriatic arthritis. The new formulation offers healthcare providers the choice to customize treatment to meet the needs of their patients. Many patients are not comfortable with self-injection so this new approval enables them to have treatment administered in a healthcare setting.[26]

VEOPOZ

Manufacturer:
Regeneron Pharmaceuticals

Approved:
August 18, 2023

Background

CHAPLE disease is an ultra-rare life-threatening immune disease driven by an overactivation of the complement system. People with CHAPLE disease have severe gastrointestinal problems, like abdominal pain and diarrhea and are prone to lung infections and severe blood clots.[27] There are fewer than 100 patients worldwide diagnosed with CHAPLE disease. Veopoz is a fully human, monoclonal antibody designed to block the activity of complement factor C5 and prevent diseases mediated by the complement pathway.[28]

RWE Use

Veopoz was approved based on results from a single-arm study in which 10 patients' outcomes were compared to pre-treatment data in patients who had hypoalbuminemia with active CD55-deficient protein-losing enteropathy (CLE). All ten patients achieved normalization of serum albumin by week 12 and maintained these concentrations through 72 weeks of treatment. All ten patients also demonstrated a reduction in the number of hospitalizations and albumin transfusions over the first 48 weeks of treatment compared to the 48 weeks prior to treatment.[29]

Approval & Impact

Veopoz is the first and only treatment indicated specifically for CHAPLE. Beyond CHAPLE disease, researchers at Regeneron Pharmaceuticals believe that Veopoz has promise to treat a variety of complement-mediated diseases.[30] The FDA granted Veopoz fast track, orphan drug, and rare pediatric disease designations.

JOENJA

Manufacturer:
Pharming

Approved:
March 24, 2023

Background

Activated PI3K-delta syndrome (APDS) is a genetic disorder that weakens the immune system and affects an estimated one to two people per million. People with this condition often have low numbers of white blood cells, particularly certain types of B cells and T cells. These cells are critical in identifying and attacking foreign viruses and bacteria to prevent infection.[31] Joenja is an oral small molecule phosphoinositide 3-kinase delta inhibitor that impedes the production of phosphatidylinositol-3-4-5-triphosphate that serves as an important cell messenger and regulates many cell functions.[32]

RWE Use

The FDA approval was based on safety and efficacy results from a 12-week randomized clinical trial of 31 patients. Also submitted as part of the application was real-world evidence from a long-term, open-label extension clinical trial in which 38 patients received Joenja for a median treatment span of two years.[33]

Approval & Impact

Joenja is the first and only treatment indicated for APDS targeted for adult and pediatric patients 12 years of age and older. Joenja promises to transform the treatment pathway for patients living with APDS who experience severe, life-altering, and progressive symptoms. FDA approval for one of more than 450 primary immunodeficiencies is also an encouraging sign for the broader primary immunodeficiency community.[34] The FDA granted Joenja orphan drug, rare pediatric disease, and priority review designations.

ZILBRYSQ

Manufacturer:
UCB

Approved:
October 17, 2023

Background

Myasthenia Gravis (gMG) is a rare autoimmune disease and the most common primary disorder of neuromuscular transmission usually the result of an acquired immunological abnormality. The disease progresses from specific muscle weakness restricted to the optical muscles or the throat and limb muscles. There are an estimated 14-20 per 100,000 cases with nearly 36,000 to 60,000 cases in the U.S. but many believe the disease is underdiagnosed, so prevalence is likely higher.[35] Zilbrysq was approved by the FDA for adult patients who are anti-acetylcholine receptor antibody-positive.

RWE Use

The FDA approved Zilbrysq based on the RAISE study, a multi-center, 3 phase randomized, double-blind, placebo-controlled study to assess safety and efficacy.[36] In addition, a phase 3 RAISE-XT open-label extension (OLE) study was conducted and showed patients maintained their response for almost 90% of their time on long-term treatments. The findings supported the early use of Zilbrysq and the long-term benefit of the treatment in a broad population of gMG patients.[37]

Approval & Impact

Zilbrysq is the first once daily self-administered targeted peptide inhibitor of complement 5 (C5) inhibitor and the only therapy for adult patients with an anti-AChR antibody-positive gMG. The ability to self-administrate compared to an IV dispensation of the treatment benefits patients by reducing travel time to and from hospitals, minimizing interference with work commitments, and increasing independence. The approval of Zilbrysq provides physician with another option for treating gMG patients. The FDA granted Zilbrysq with orphan drug designation.

ELFABRIO

Manufacturer:
Chiesi Global Rare Diseases/Protalix

Approved:
May 9, 2023

Background

Fabry disease is an inherited neurological disorder that occurs when the enzyme alpha-galactosidase-A fails to efficiently break down fatty materials known as lipids into smaller components that provide energy to the body. The mutated gene causes lipids to build up harmful levels that negatively effect involuntary functions like breathing and heartbeat as well as the eyes, kidneys, and cardiovascular system.[38] There is a wide estimate as to how many people suffer from Fabry disease ranging from one in every 17,000 to one in every 117,000.[39] Elfabrio is an enzyme replacement therapy that results in a molecule with stable pharmacokinetic parameters.[40]

RWE Use

The safety, tolerability, and effectiveness of Elfabrio was studied in a long-term open label extension of more than 140 patients with up to 7.5 years of follow up treatment. Over that period, Elfabrio demonstrated consistent and robust efficacy findings in treatment-naïve patients. The drug was also studied in the BALANCE trial, a two year, active control study.[41]

Approval & Impact

While much progress has been made in developing treatments for Fabry Disease, the approval of Elfabrio provides physicians with another effective option. Elfabrio is the first plant-based enzyme replacement therapy which enables it to deliver a functional version of the Gal A enzyme directly into a patient's bloodstream.[42] The development of Elfabrio is a significant milestone in the pursuit of a durable therapy for Fabry Disease.[43] The FDA granted Elfabrio fast track designation.

PSYCHIATRIC

EXXUA

Manufacturer:
Fabre-Kramer Pharmaceuticals

Approved:
September 22, 2023

Background

Major Depressive Disorder (MDD) is the most diagnosed form of depression. More than 20 million adults in the U.S. experienced a major depressive disorder each year prior to the COVID-19 pandemic. During the pandemic, this number jumped to more than 80 million experiencing elevated symptoms of depression. Exxua is a novel oral selective serotonin (5HT) 1a receptor agonist that treats major depressive disorder in adults.[44]

RWE Use

Exxua approval was based on two eight-week placebo-controlled studies and an open-label phase collecting real-world evidence from 5,000 patients over a 12 month period which showed that the anti-depressant could effectively relieve depressive symptoms with acceptable side effects.[45]

Approval & Impact

Exxua is the first and only oral selective 5HT 1a receptor agonist for treatment of MDD. The drug is an important milestone in the treatment of MDD by providing physicians and patients with a wide range of treatment options. Exxua fills an important need for new mechanisms of action to treat the disorder and is being developed for other psychiatric disorders.[46] FDA granted Exxua fast track designation.

HEPATOLOGY

RIVFLOZA

Manufacturer:
Novo Nordisk

Approved:
September 29, 2023

Background

Primary hyperoxaluria (PH) is a rare genetic disease that causes the liver to overproduce oxalate. PH1, the most clinically severe of three PH subtypes affecting 80% of PH patients, is a progressive metabolic disorder that can lead to progressive kidney disease. The disorder is estimated to affect one in 38,600 patients worldwide. Rivfloza is a once-monthly subcutaneous ribonucleic acid interference therapy indicated to lower urinary oxalate levels in individuals nine years of age or older.[47]

RWE Use

FDA approval of Rivfloza was based on results from a phase 2 PHYOX 2 clinical trial and interim real-world data from an ongoing phase 3 PHYOX 3 extension study. The extension study results showed effectiveness was maintained in 13 patients with PH1 who received an additional six months of treatment with Rivfloza.[48]

Approval & Impact

Rivfloza provides clinicians with a novel treatment that lowers oxalate production safely and effectively. Patients with PH1 now have more choices when working with their providers to determine the best treatment pathway.[49] The FDA granted Rivfloza orphan drug and rare pediatric disease designations.

NEUROMUSCULAR

AGAMREE

Manufacturer:
Santhera

Approved:
October 26, 2023

Background

Duchenne Muscular Dystrophy (DMD) is associated with the most severe clinical symptoms of all muscular dystrophies. It is caused by a genetic mutation on one of the mother's X chromosomes. The disease affects boys and occurs in one in 3,500 to 5,000 newborns. Agamree is a dissociative steroid that is a novel treatment for DMD. Steroids are considered standard of care for DMD since they significantly slow the disease progression. The mechanism of Agamree reduces steroid side effects and makes treatment more tolerable.[51]

RWE Use

The FDA's approval of Agamree was based on the results from a Phase 2b VISION-DMD study. Safety information was obtained from real-world evidence collected from three open-label studies, including extension studies.[52] Agamree was administered orally once daily for 24 months to young boys with DMD.[53]

Approval & Impact

Agamree is the first drug fully approved in both the U.S. and Europe for the treatment of patients with DMD.[54] The approval of Agamree is significant since it is used to treat DMD regardless of the specific genetic mutation. The drug provides anti-inflammatory and muscle strengthening benefits with decreased side effects such as bone fragility, delayed growth, insulin resistance, and behavior changes.[55] Agamree was granted orphan drug, and rare pediatric disease designations by the FDA.

AUGTYRO

Manufacturer:
Bristol Meyers Squibb

Approved:
November 15, 2023

Background

Lung cancer is the leading cause of cancer deaths in the U.S. with non-small cell lung cancer (NSCLC) making up 85% of diagnoses. ROS1 fusions are rare and occur in about 1%-2% of patients with NSCLC. ROS1-positive lung cancer is often extremely aggressive, and many times can spread to the brain.[56] Augtyro is the first FDA approval that includes patients with ROS1-positive non-small cell lung cancer who have previously received a ROS1 tyrosine kinase inhibitor, as well as patients who are tyrosine kinase inhibitor naïve.[57]

RWE Use

The FDA approved Augtyro based on TRIDENT-1, a global, multicenter, single-arm, open-label, multi-cohort clinical trial.[58] The trial didn't compare the drug to a placebo and researchers knew which experimental drug they were using.[59] Patients were followed for duration of response for up to 3 years.[60]

Approval & Impact

New treatment options for patients with ROS1 fusion-positive NSCLC are urgently needed. Augtyro is the only approved next-generation TK1 for ROS1-positive NSCLC patients and may possibly become the new standard of care for these patients.[61] The application was granted priority review, breakthrough, and fast track designations by the FDA.

TEMODAR

Manufacturer:
Merck

Approved:
September 15, 2023

Background

Anaplastic astrocytoma is a rare, malignant brain tumor that arises from astrocytes, the supportive cells in the nervous system, and belongs to the broader category of gliomas. Anaplastic astrocytomas are rare, affecting about 1%-2% of all primary brain tumors. An estimated 1,570 new cases were diagnosed in 2017.[62] Temodar was first approved in 1999 in capsule form with a newly diagnosed glioblastoma indication granted in 2005.[63] The FDA recently approved an updated label for Temodar for two new and three revised indications.[64]

RWE Use

Temodar was approved for these label expansions as part of the Project Renewal initiative from the Oncology Center of Excellence. Oncology experts and scientists review existing published literature to evaluate real-world evidence for independent FDA review. Project Renewal is limited to updating labeling of drugs with decades of use through research of supportive clinical studies and substantial marketing experience.[65]

Approval & Impact

Project Renewal's goal is to update labeling information for older oncology drugs to ensure information is clinically meaningful and scientifically up to date. Temodar is the second drug to receive approval for a label expansion under this pilot program.[66]

ANALGESICS

NARCAN

Manufacturer:
Emergent BioSolutions

Approved:
March 29, 2023

Background

The U.S Centers for Disease Control and Prevention estimates that 107,000 Americans died because of a drug overdose in 2021. More than 70,000 were caused by the use of synthetic opioids containing fentanyl. The increased fatalities along with the growth of fentanyl has spurred the need to expand access to opioid overdose reversal treatment.[67] To meet this growing challenge, the FDA approved the label expansion of the Narcan nasal spray for over-the-counter, non-prescription use.[68]

RWE Use

Narcan nasal spray was first approved by the FDA in 2015 as a prescription drug.[69] Since 2016, more than 44 million doses have been distributed. The new OTC product will have the same formulation, device design, and original prescription strength of 4 mg. The FDA's approval of prescription-to-OTC was supported by Human Factors study data, an updated Drug Facts label, real-world pharmacovigilance data collected from various public sources, and seven years of real-world post-marketing safety data.[70]

Approval & Impact

Narcan OTC is the first naloxone product approved for use without a prescription. The approval paves the way for life-saving medication to reverse an opioid overdose by enabling sales directly to consumers in drug stores, convenience stores, grocery stores, gas stations, and online.[71]

CARDIOVASCULAR

LEQVIO

Manufacturer:
Novartis

Approved:
July 10, 2023

Background

Cardiovascular disease (CVD) is the leading cause of death in the U.S., greater than all types of cancer, unintentional injury, and stroke combined. High levels of primary hyperlipidemia (high LDL-C) is a key risk factor for CVD and one of the most easily lowered through medication. The FDA approved Leqvio in December 2021 after three randomized, double-blind, placebo-controlled trials proved its effectiveness. In July 2023, the FDA approved the use of Leqvio earlier in LDL-C treatment as an add-on to diet and statin therapy.[72]

RWE Use

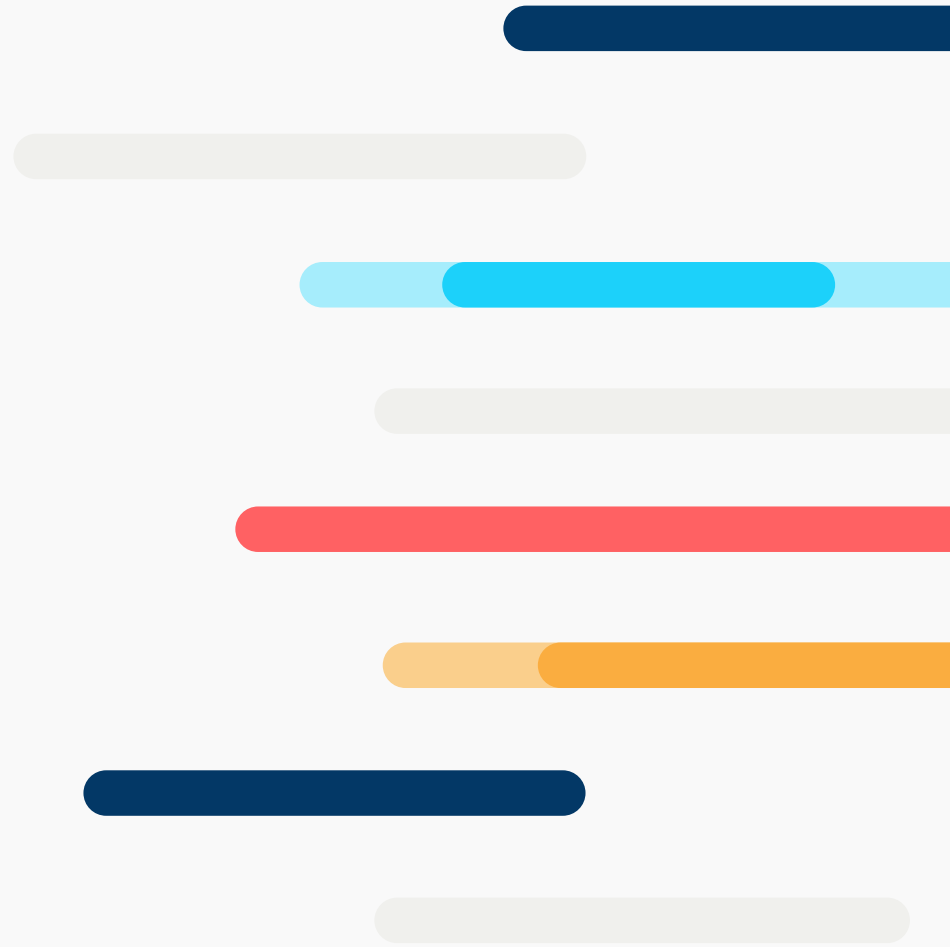
The label expansion approval was supported by data from the VictORION clinical trial program, one of the largest cardiovascular clinical trial programs. VictORION includes 27 trials and is designed to collect comprehensive real-world data from more than 60,000 patients in more than 50 countries worldwide.[73]

Approval & Impact

When approved in 2021, Leqvio was the first and only small interfering RNA therapy to lower LDL-C. The label expansion enables broader use and earlier treatment for those patients with elevated LDL-C but who have not yet had a cardiovascular event. The label expansion includes removal of Limitations of Use statement and the safety section that listed four adverse reactions that were proven to be no more prevalent than in the placebo arm.[74]

SUMMARY

The growing use of RWD and RWE in regulatory decision making is rapidly making effective drugs available, especially for rare diseases. Support from RWE is also instrumental in label expansions for existing approved drugs, in many cases widening availability to a larger patient population and enabling use of treatment early in the treatment lifecycle. Researchers and regulators will be increasingly relying on real-world data to streamline approvals and get life-saving drugs to patients who need them even sooner.



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