From data to impact: Exploring the evolution of real-world evidence at the FDA

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Abstract:
The healthcare industry has witnessed a significant shift towards the use of real-world data (RWD) and real-world evidence (RWE) in medical decision-making and treatment evaluation. This article explores the importance of RWE in healthcare decision-making and its potential to revolutionise drug development, regulatory processes, and patient care. We examined the US FDA's strategic vision for RWD and RWE, tracing the agency's evolving stance from early 2000s to present day. The FDA's framework for RWE, key guidance documents, and the establishment of the Center for Real-World Evidence Innovation are discussed. Case studies illustrate RWE's role in supporting regulatory decisions, including safety labelling changes and label expansions. We conclude by discussing the future of RWE, including its integration with artificial intelligence and its importance in evaluating cell and gene therapies, emphasising its transformative impact on healthcare innovation and regulatory processes.

Introduction

In recent years, the healthcare industry has undergone a significant shift in the methods used for medical decision-making and treatment evaluation. Leading this transformation is the growing acceptance of real-world data (RWD) and real-world evidence (RWE). This article explores the importance of RWE in healthcare decision-making and their potential to revolutionise drug development, regulatory processes, and patient care. In this context, the article will also examine the US FDA strategic vision for RWD and RWE.

RWD refers to all health-related information collected outside of traditional clinical trial settings and includes electronic health records, claims databases, as well as data from wearables, social media, and a variety of other sources; whereas RWE is the clinical evidence derived from the analysis of RWD. RWE provides valuable insights into real-world treatment patterns and unmet medical needs, helping to prioritise research efforts and allocate resources more effectively. Real-world research is particularly valuable for evaluating safety and effectiveness in rare or severe diseases, paediatric populations, or other patient groups often underrepresented in clinical trials, as it allows for an understanding of treatment effects in diverse patient populations receiving care in conventional settings. RWD can also support post-marketing surveillance, helping to identify emerging safety signals and long-term safety or to describe treatment outcomes among patients treated off-label. In regulatory approvals, RWE has been used to confirm the effectiveness of drugs approved under accelerated pathways, support label expansions, and provide contextual data for single-arm trials.

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RWE: FDA history and guidance

RWD and drug safety

The FDA has a long-standing history of utilising RWD and RWE for post-market safety monitoring. The FDA's evolving stance on RWE can be traced back to the early 2000s, with a notable milestone being the Prescription Drug User Fee Act (PDUFA) III in 2002. PDUFA III introduced user fees to expedite drug reviews and, in recognition that electronic healthcare data sources were becoming a valuable source for medical research, the act included provisions for considering observational data in regulatory decisions related to drug safety. This act laid the groundwork for the FDA's gradual integration of RWE into its regulatory framework.[1] The agency's Sentinel Initiative, launched in 2008, is a prime example of this approach. Sentinel uses a standard data model to combine various sources of insurance claims data and electronic health records (EHRs) to evaluate the safety of medical products after they have been approved and are in use in the general population.[2] The FDA has also used RWE in the context of rare diseases and paediatric populations, where conducting large-scale randomised clinical trials may be infeasible or unethical. For example, the agency has considered RWE from natural history studies and patient registries to support the approval of treatments for rare genetic disorders.[3]

Framework for RWE

The 21st Century Cures Act, signed into law in 2016, has significantly shaped the FDA's approach to evaluating and using RWE. This legislation mandated the FDA to establish a programme to evaluate the potential use of RWE to support approval of new indications for approved drugs or to satisfy post-approval study requirements.[4] Importantly, the Cures Act explicitly enabled the FDA to consider RWD in assessing drug effectiveness, expanding the potential applications of RWE beyond its traditional role in safety monitoring.

Key aspects of the FDA's RWE framework include:

- Ensuring transparency in the use of RWE for regulatory purposes.
- Defining appropriate use cases for RWE in regulatory decision-making.
- Establishing standards for data quality and reliability.
- Developing methodologies for analysing and interpreting RWE.

Image: Freepik

The framework emphasises the importance of data quality, study design, and analytical methods in generating reliable and relevant RWE. It also acknowledges the need for transparency in the use of RWE and the importance of stakeholder engagement in developing standards and best practices.[5]

Guidance documents

To support the implementation of its RWE framework, the FDA has issued several guidance documents that provide detailed recommendations on various aspects of RWE use in regulatory decision-making.

These guidance documents provide stakeholders with clear expectations and methodological considerations for using RWD and RWE in regulatory submissions. They address issues such as data collection and quality, study design, and analytical methods, helping to ensure that RWE is reliable, relevant, and appropriately integrated into the regulatory process.[6]

Key FDA guidance documents[6] include:

- **Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices.**[7] This document focuses on how RWD and RWE can be used in regulatory decisions for medical devices. It covers aspects such as approval, labeling changes, and post-marketing surveillance.
- **Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics.**[8] This guidance offers recommendations to sponsors on submitting documents containing RWD and RWE to the FDA. It focuses on the evaluation process for drugs and biological products using real-world information.
- **Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products.**[9] This guidance offers recommendations on evaluating the relevance and reliability of EHR and medical claims data for generating RWE. It focuses on using these data sources to support regulatory decisions for drugs and biologics.
- **Data Standards for Drug and Biological Production Submissions Containing Real-World Data.**[10] This document establishes standardised data formats and requirements for RWD submissions in regulatory applications. It aims to ensure consistency and reliability in the evaluation process of drug and biological products.
- **Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products.**[11] This document provides recommendations on designing, conducting, and analysing externally controlled trials. It focuses on using these trials to support regulatory decisions for drugs and biological products

A comprehensive list of FDA RWE guidance is currently available on the agency's website.[6]

The FDA's guidance emphasises the importance of data quality, including considerations such as data provenance, completeness, and accuracy. It also addresses methodological considerations for study design and analysis, recognising that the observational nature of much RWD requires careful attention to

potential biases and confounding factors.

Furthermore, the FDA's guidance documents highlight the Agency's commitment to an evolving healthcare system, where insights from routine clinical practice can inform regulatory decision-making and vice versa. This approach aims to create a more efficient and responsive regulatory process that can keep pace with rapid advancements in medical science and technology.

Additionally, the FDA Center for Drug Evaluation and Research (CDER) established the Center for Real-World Evidence Innovation (CCRI) in December 2024, marking a significant step in the Agency's commitment to advancing the use of RWE in regulatory decision-making. The objective of the CCRI is to promote and facilitate the use of RWE in drug development and regulatory processes, enhancing the efficiency and effectiveness of drug evaluation and approval. The CCRI was created in response to the increasing role of RWE in drug development and the need for a coordinated approach to its evaluation and integration in regulatory processes. This initiative is expected to significantly influence how RWE is utilised in drug approvals, potentially leading to more efficient and patient-centric regulatory decisions. The CDER CCRI insights are expected to inform future FDA policies and guidelines on RWE use, providing clearer direction to regulators and pharmaceutical companies regarding the design and analysis of fit-for-purpose RWE studies intended to support regulatory decision-making.[12]

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Case studies: RWE in decision making

The FDA has increasingly recognised the value of RWE in supporting faster and more informed regulatory decisions. RWE can provide additional evidence to support drug approvals, label expansions, or post-market safety monitoring.

Case study (safety labelling): Fluroquinolones

RWD data studies have played a crucial role in supporting labelling changes for fluoroquinolones regarding various safety issues. Fluroquinolones are a class of antibiotics sometimes used to treat acute bacterial sinusitis, bronchitis, and urinary tract infections; though due to the safety concerns, the current label states they should only be prescribed when patients have no alternative treatment options. RWD studies significantly contributed to the body of evidence that supported the FDA's decision to add boxed warnings regarding tendon rupture associated with fluoroquinolone use in 2008, for worsening symptoms of myasthenia gravis in 2010, and for irreversible peripheral neuropathy in 2013. RWD was also displayed at an FDA advisory committee meeting in 2015 demonstrating fluoroquinolones were widely used despite current restrictive labeling.[13] The meeting evaluated results from multiple real-world studies assessing safety issues spanning peripheral neuropathy,[14] retinal detachment,[15] tendon rupture,[16] cardiac arrhythmia,[17] and aortic aneurysm.[18] These RWD studies complemented data from clinical trials and spontaneous adverse event reports, providing a more comprehensive picture of the safety profile of fluoroquinolones in real-world use resulting in multiple regulatory actions aimed to evaluate the risks and benefits of these antibiotics.

Case study (safety labelling): Methotrexate

Methotrexate is used to treat a variety of conditions including certain forms of lymphoma, breast cancer, as well as certain autoimmune diseases, such as rheumatoid arthritis and refractory psoriasis. Though effective, the drug is associated with high toxicity and severe side effects, including death, especially when taken too frequently. In 2019, the FDA leveraged its Sentinel system to investigate dosing errors among patients with rheumatoid arthritis with new use of methotrexate. The study estimated that 0.4% of patients experienced an overdose requiring rescue therapy.[19] These findings, combined with adverse event reports, prompted the FDA to mandate changes to methotrexate's prescribing information. The required modifications included a new warning about dosing error risks, clarification of the dosing schedule for non-oncologic uses, and the development of patient medication guides.

Case study (label expansion): Ibrance

In 2019, the FDA set another significant precedent in the use of RWE by approving a supplemental New Drug Application (sNDA) for Ibrance (palbociclib) in male breast cancer patients. This approval was based on information from clinical trials supplemented by RWE derived from electronic health records in the Flatiron Health database. The RWE study demonstrated that Ibrance's safety and effectiveness profile in male patients was consistent with that observed in female patients, supporting the drug's use case for treating male patients with breast cancer.[20] The RWD-based study was able to provide evidence for expanding Ibrance's use more rapidly than would have been possible through traditional clinical trials, accelerating patient access to this treatment. The FDA's decision showcases regulatory flexibility in considering alternative evidence sources and underscores the value of large-scale EHR databases in generating regulatory-grade evidence, particularly for rare conditions or underrepresented patient groups.

Case study (label expansion): Prograf

In July 2021, the FDA made a landmark decision by approving Prograf (tacrolimus) for preventing organ rejection in lung transplant patients, based solely on RWE. This groundbreaking approval utilised data from the U.S. Scientific Registry of Transplant Recipients, comparing Prograf-based immunosuppression to cyclosporine-based regimens in adult and paediatric patients who received lung transplants.[21] The study focused on patient and graft survival at 1-year post-transplantation. Results demonstrated improved outcomes with Prograf, including higher 1-year survival rates, while maintaining a safety profile consistent with its known effects in patients who received other organ transplant. This decision not only expanded treatment options for lung transplant recipients but also set a new precedent for the use of high-quality registry data in regulatory approvals. Thus, by leveraging RWE from a large patient registry, the FDA validated the potential of RWD to inform regulatory decisions.

Conclusion

The FDA has progressively integrated RWE into its regulatory framework, evolving from its initial use in post-marketing safety monitoring to a more comprehensive approach. This evolution

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was marked by key legislative milestones such as the Prescription Drug User Fee Act III in 2002 and the 21st Century Cures Act in 2016. The FDA's RWE framework emphasises transparency, data quality, and appropriate methodologies for analysing and interpreting RWD. To support this framework, the FDA has issued numerous guidance documents addressing various aspects of RWE use in regulatory decision-making. These documents provide stakeholders with clear expectations and methodological considerations for using RWE in regulatory submissions. The FDA's approach recognises the potential of RWE to inform regulatory decisions throughout a product's lifecycle, from approval of new indications to post-approval studies. The establishment of the CCRI in 2024 further demonstrates the FDA's commitment to advancing RWE use in drug development and regulatory processes. This evolving stance reflects the FDA's adaptation to a changing healthcare landscape, where insights from routine clinical practice can significantly inform regulatory decision-making.

Looking ahead, the increasing use of RWE is expected to lead to more efficient drug development, faster regulatory approvals, and improved patient outcomes by bridging the gap between clinical trials and real-world practice. As technology and data analytics continue to advance, RWE is set to become increasingly central in driving the future of healthcare and medical innovation. The integration of artificial intelligence with RWE will revolutionise our ability to identify patterns, predict outcomes, and personalise treatments. Artificial intelligence algorithms can sift through vast amounts of RWD to generate hypotheses, design more targeted clinical trials, and may even predict potential safety issues before they emerge in clinical practice. RWE will be crucial in understanding long-term efficacy and safety profiles of upcoming cell and gene therapies, given the novelty, complexity, and potentially curative nature of these treatments. As these innovative therapies often target rare diseases or specific genetic profiles, RWE can provide valuable insights into their real-world performance across diverse patient populations and healthcare settings. Moreover, RWE will be instrumental in addressing the unique challenges posed by these therapies, such as durability of response and potential long-term side effects, which may not be fully captured in traditional clinical trials. By leveraging RWE, regulators and healthcare providers are better equipped to make informed decisions regarding the utilisation, safety, effectiveness, and value of cutting-edge treatments, ultimately accelerating the path from scientific breakthroughs to patient benefit.

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Disclosures and conflicts of interest

The authors declare no conflicts of interest.

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