How regulatory guidance on real-world evidence changed drug submissions

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

The pharmaceutical industry has long relied on the pristine, controlled environment of randomised controlled trials (RCTs) to demonstrate drug efficacy and safety. But the real world, with its diverse patient populations, varying adherence, and complex comorbidities, often tells a different story. Regulators, recognising this gap, have steadily evolved their stance on real-world evidence (RWE), shifting how sponsors approach drug development and post-market surveillance.

KEY TAKEAWAYS

- The Pivot: Regulatory bodies now expect sponsors to proactively integrate RWE into drug development, not just as post-market observations.
- The Data: RWE is increasingly used to support label expansions, inform trial design, and provide context for drug safety profiles.
- The Action: Clinicians should expect future drug approvals and guideline updates to be increasingly informed by data reflecting routine clinical practice.

Traditional clinical trials, while the gold standard for establishing causality, often operate under highly selective inclusion and exclusion criteria. This can create a disconnect between the trial population and the patients seen in everyday practice, limiting the generalisability of findings. The inherent artificiality of a trial setting, from strict dosing schedules to intensive monitoring, does not always translate to the complexities of real-world adherence and polypharmacy. This gap has driven the push for more comprehensive data, moving beyond just efficacy in ideal conditions to effectiveness in typical ones.

Sponsors historically viewed real-world data (RWD) primarily as a tool for post-market safety surveillance or for generating hypotheses for future trials. This perspective has undergone a significant transformation, driven by evolving regulatory expectations. The shift is not merely about collecting more data; it is about integrating RWD and RWE strategically throughout the product lifecycle, from early development to market access and label expansion. This requires a more sophisticated approach to data collection, analysis, and interpretation, moving beyond simple observational studies to more robust methodologies capable of addressing confounding factors.

The Evolving Regulatory Guidelines

Regulatory agencies have progressively issued guidance documents outlining their expectations for the use of RWE. These guidances clarify the types of RWD considered acceptable, the methodological standards for generating RWE, and the specific contexts in which RWE can support regulatory decisions. The emphasis has moved from merely accepting

RWE as supplementary information to actively encouraging its use in specific scenarios, such as informing external control arms for single-arm trials or supporting indications in rare diseases where large RCTs are impractical. This evolution reflects a growing confidence in the ability of well-designed RWE studies to provide valuable insights into drug performance outside of controlled settings.

The European Medicines Agency (EMA), for instance, has published frameworks detailing how RWE can be used to support regulatory submissions, particularly for post-authorisation efficacy and safety studies. These frameworks highlight the importance of data quality, transparency, and appropriate analytical methods to minimise bias. The agency's scientific advice procedures now frequently include discussions on RWE generation plans, indicating a proactive engagement with sponsors on this front. This means that sponsors are now expected to consider RWE generation as an integral part of their development strategy, rather than an afterthought. The regulatory guidance on real-world evidence has fundamentally altered the content of drug submissions.

What Sponsors Submit Now

The practical consequence of these evolving guidelines is a noticeable change in the content and structure of regulatory submissions. Sponsors are now incorporating RWE in several key areas. They use RWD to characterise disease epidemiology and natural history, providing essential context for unmet medical need and patient populations, which is important for ensuring trials address clinically relevant questions. This can help define appropriate endpoints and patient subgroups for interventional trials, ensuring that the trials are designed to address clinically relevant questions. For example, understanding the real-world progression of a rare disease can inform the selection of a meaningful primary endpoint that might not be obvious from smaller, earlier studies.

RWE is also increasingly used to support external control arms, particularly in situations where randomising patients to placebo or standard of care is ethically challenging or logistically difficult. This is common in oncology or rare diseases, where patient numbers are limited. The methodological rigour required for such applications is substantial, demanding careful matching of patient characteristics and statistical adjustments to account for differences between the RWD cohort and the interventional arm. The potential for real-world evidence studies to overstate drug benefits due to confounding by indication remains a significant concern, necessitating stringent analytical approaches.

RWE plays a critical role in demonstrating the effectiveness of drugs in broader, more heterogeneous patient populations than those typically enrolled in RCTs. This includes patients with comorbidities, those on concomitant medications, or individuals with varying levels of adherence. Such data can strengthen a drug's value proposition and support label expansions for new indications or patient subgroups. For instance, if a drug is approved for a specific type of cancer, RWE might be used to show its benefit in a different stage of the disease or in patients with specific genetic mutations not fully represented in the main trials. This requires careful consideration of data sources, from electronic health records to claims databases, and an understanding of their inherent biases and limitations.

Challenges and Opportunities

Despite the growing acceptance, challenges persist in the generation and regulatory acceptance of RWE. Data quality remains a paramount concern; RWD is often collected for purposes other than research, leading to missing data, inconsistencies, or lack of granular detail. Methodological challenges, particularly in controlling for confounding and selection bias, require advanced statistical techniques and transparent reporting. Regulators demand clear justifications

for data sources, analytical methods, and assumptions made during RWE generation. The scrutiny of patient-reported outcomes, for example, highlights the need for robust validation when integrating such data into RWE studies.

The opportunity, however, is substantial. RWE can accelerate drug development by informing trial design, reducing the need for lengthy and expensive RCTs in certain contexts, and providing a more complete picture of a drug's benefit-risk profile in routine clinical practice. It can also support market access decisions by demonstrating real-world value to payers and health technology assessment bodies. The integration of RWE into regulatory submissions reflects a pragmatic recognition that while RCTs are indispensable, they do not tell the whole story. A comprehensive understanding of a drug's performance requires data from both controlled and uncontrolled environments. Clinicians often consult resources like the Oxford Handbook of General Practice, 5th Edition for quick reference on established treatments, but RWE is increasingly shaping the evidence base for newer therapies.

The future of drug development will likely see an even greater synergy between RCTs and RWE. Hybrid approaches, where RWD is used to augment or contextualise RCT findings, are becoming more common. This could involve using RWD to monitor long-term safety outcomes beyond the trial period or to compare the effectiveness of a new drug against real-world comparators. The goal is to move towards a more holistic evidence generation paradigm that leverages the strengths of both approaches, providing a more accurate and comprehensive understanding of medical interventions for patients and prescribers.

CLINICAL IMPLICATIONS

The shift in regulatory guidance on real-world evidence means clinicians will increasingly encounter drugs whose approval or label expansion was supported by data reflecting everyday practice, not just highly controlled trials. This should, in theory, lead to a better understanding of how these therapies perform in the heterogeneous patient populations seen in clinics, including those with multiple comorbidities or complex medication regimens. The data should feel more relevant to the patients sitting in front of us.

But this also places a greater onus on clinicians to critically evaluate the source and methodology of the RWE presented. Not all real-world data is created equal; biases inherent in observational studies, such as confounding by indication or selection bias, can distort perceived benefits or risks. A healthy skepticism, coupled with an understanding of basic epidemiological principles, remains essential when interpreting these findings.

For the pharmaceutical industry, the message is clear: RWE is no longer a peripheral activity. It is a core component of evidence generation, demanding early strategic planning and investment in strong data infrastructure and analytical capabilities. Companies that fail to adapt will find themselves at a disadvantage in a regulatory environment that increasingly values a comprehensive, real-world perspective on drug performance.

This evolution aims to bridge the gap between clinical research and clinical practice. If executed well, the increased reliance on RWE should provide a more complete picture of a drug's utility, allowing for more informed prescribing decisions and, ideally, better patient outcomes in the messy reality of healthcare delivery.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Dasgupta A, Kaushik A, Pandey S, Attri S, Miller P, Tolley K. A Review of the Utilization of Relative Dose Intensity and Dose Delay Factor in Health Technology Appraisals of Oncology Drugs in Solid Tumors. Adv Ther. 2025;42(11):5313-5340. doi:10.1007/s12325-025-03358-6

LICENCE & RIGHTS

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com