Real-world evidence: How regulators changed what sponsors submit

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

The market of drug development and regulatory approval has always been defined by the gold standard of randomized controlled trials (RCTs). These trials offer unparalleled internal validity, meticulously controlling for confounding variables to isolate a treatment's effect. But the real world, with its heterogeneous patient populations, varied adherence patterns, and complex comorbidities, rarely mirrors the pristine conditions of an RCT. This fundamental disconnect has driven a sustained push for the integration of real-world evidence (RWE) into regulatory decision-making, a shift that has profoundly reshaped how sponsors approach their submissions.

KEY TAKEAWAYS

- The Pivot: Regulatory bodies now actively encourage, and in some cases require, the submission of real-world evidence to supplement traditional clinical trial data.
- The Data: RWE can encompass electronic health records, claims data, patient registries, and even data from wearable devices, offering insights into treatment effectiveness and safety in routine clinical practice.
- The Action: Clinicians should expect to see more label expansions and post-market safety updates informed by RWE, providing a broader understanding of drug performance outside of controlled trial settings.

For decades, the path to drug approval was largely linear: preclinical studies, followed by a series of increasingly larger and more complex clinical trials, culminating in a New Drug Application (NDA) or Marketing Authorisation Application (MAA) built predominantly on RCT data. This approach, while robust for establishing efficacy and safety under ideal conditions, often left gaps regarding a drug's performance in broader, less selected patient groups, or over longer durations than typical trial follow-up. The unmet need for a more comprehensive understanding of drug performance in everyday clinical practice became increasingly apparent, particularly as healthcare systems grappled with rising costs and the imperative for value-based care.

Regulators, including the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), recognized this limitation. They began to explore how data generated outside of conventional clinical trials could complement the existing evidence base. This 'real-world data' (RWD) includes information routinely collected during patient care, such as electronic health records (EHRs), administrative claims data, disease registries, and even data from patient-generated sources like wearable devices. When these data are analyzed to generate evidence on product use and potential benefits or risks, they become real-world evidence (RWE).

The Evolution of Regulatory Expectations

The shift towards integrating RWE into regulatory submissions did not happen overnight. It was a gradual evolution, driven by technological advancements in data collection and analysis, alongside a growing recognition of the limitations of relying solely on RCTs. Early guidance documents from regulatory bodies focused on defining what constituted RWD and RWE, establishing standards for data quality, and outlining appropriate methodologies for its generation and analysis. These initial frameworks aimed to build confidence in RWE, ensuring its reliability and relevance for regulatory decisions.

One of the primary drivers for this change was the need to understand drug safety and effectiveness in diverse populations. RCTs often exclude patients with significant comorbidities, those on multiple concomitant medications, or individuals from specific demographic groups. This selectivity, while necessary for internal validity, limits the generalizability of trial results. RWE, by drawing from vast populations receiving care in routine settings, can provide insights into how a drug performs across the full spectrum of patients who might eventually receive it. This broader perspective is invaluable for identifying rare adverse events or for understanding differential treatment effects in subgroups not adequately represented in trials.

Another key area where RWE has proven instrumental is in post-market surveillance. After a drug is approved, continued monitoring for safety and effectiveness is essential. Traditional post-market studies can be resource-intensive and slow. RWD, particularly from claims databases and EHRs, offers a more efficient and comprehensive way to track drug performance over extended periods and in large populations. This allows regulators to detect emerging safety signals or confirm long-term benefits more rapidly than would be possible with dedicated prospective studies. The ability to leverage existing data infrastructure for these purposes represents a significant efficiency gain for both regulators and sponsors.

How Sponsors Adapted Their Submissions

The evolving regulatory guidelines compelled pharmaceutical sponsors to fundamentally rethink their evidence generation strategies. No longer could they rely solely on a package of RCTs. Instead, they began to incorporate RWE at various stages of the drug development lifecycle, from informing trial design to supporting label expansions and post-market commitments. This integration required new capabilities within companies, including expertise in epidemiology, biostatistics, health informatics, and regulatory science specific to RWE.

In some cases, RWE is now used to support initial drug approvals, particularly for rare diseases or in situations where conducting large RCTs is impractical or unethical. For instance, single-arm studies augmented by external control arms derived from RWD have been accepted for certain orphan drugs. This approach allows for faster access to treatments for conditions with high unmet medical need, while still providing a robust comparative assessment of efficacy. The rigor applied to selecting and analyzing these external control groups is paramount, demanding careful matching of patient characteristics and disease severity to minimize bias.

More commonly, RWE serves to strengthen existing evidence or to address specific regulatory questions. Sponsors might submit RWE to support an expanded indication for an already approved drug, demonstrating its effectiveness in a new patient population or for a different stage of disease. This can be particularly valuable when the new indication is for a condition with a well-established standard of care, making a placebo-controlled RCT difficult to justify. RWE can also be used to provide context for clinical trial results, showing how the trial population compares to the real-world patient population, or to estimate the real-world impact of a treatment effect observed in an RCT.

The quality of the RWD itself is a critical consideration. Regulators demand transparency regarding data sources, collection methods, and any transformations applied to the data. Data provenance, completeness, accuracy, and relevance are all scrutinized. Sponsors must demonstrate that the RWD used is fit-for-purpose, meaning it is appropriate for answering the specific regulatory question at hand. This often involves extensive data validation and characterization, a process that can be as rigorous as the conduct of a traditional clinical trial. For example, ensuring accurate diagnostic codes in claims data or complete medication histories in EHRs requires careful attention to detail.

Challenges and Ongoing Evolution

Despite the clear benefits, the integration of RWE is not without its challenges. One persistent issue is confounding by indication, where patients receiving a particular treatment may differ systematically from those who do not, making it difficult to attribute observed outcomes solely to the treatment. Advanced statistical methods, such as propensity score matching and instrumental variable analysis, are employed to mitigate these biases, but they cannot eliminate them entirely. The inherent observational nature of most RWD means that causal inference is always more complex than in a randomized setting.

Another challenge lies in data interoperability and standardization. RWD comes from disparate sources, often collected using different coding systems and formats. Harmonizing these diverse datasets into a coherent and analyzable form requires significant effort and sophisticated computational tools. Regulatory bodies are actively working with industry and academic partners to develop common data models and standards to facilitate the use of RWD, but this remains an ongoing endeavor. The misinterpretation of FDA guidance on machine learning in biopharma highlights the complexity of applying advanced analytical techniques to these varied datasets.

The ethical implications of using RWD also warrant careful consideration. Patient privacy and data security are paramount. While RWD is typically de-identified before analysis, concerns about re-identification and the appropriate use of patient data persist. Regulatory frameworks, such as the General Data Protection Regulation (GDPR) in Europe, provide strict guidelines for data protection, but their application to large-scale RWD analyses can be complex. Sponsors must navigate these ethical and legal considerations with utmost care, ensuring patient trust is maintained.

The future of RWE in regulatory submissions will likely see continued refinement of methodologies, greater standardization of data, and an expanded role for patient-generated health data. As technology advances, data from wearables, remote monitoring devices, and patient-reported outcomes will offer even richer insights into the patient experience and treatment effectiveness. This will further blur the lines between traditional clinical trials and real-world evidence generation, moving towards a more integrated and dynamic approach to understanding drug performance.

For clinicians, this means a more complete picture of the therapies they prescribe, moving beyond the idealized trial setting to reflect the complexities of their daily practice. The impact of IVUS guidance on PCI outcomes, for example, demonstrates how real-world procedural data can inform best practices.

> **CLINICAL IMPLICATIONS**
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> The growing reliance on real-world evidence by regulatory bodies means clinicians will increasingly encounter drug labels and clinical guidelines informed by data beyond the traditional randomized controlled trial. This shift offers a more complete understanding of how therapies perform in heterogeneous patient populations, reflecting the complexities of everyday practice rather than the controlled environment of a trial. It should lead

to more relevant prescribing information, particularly regarding safety profiles and effectiveness in specific subgroups.

For pharmaceutical sponsors, the message is clear: RWE is no longer an optional add-on but an integral component of a comprehensive evidence package. This necessitates investment in data infrastructure, advanced analytical capabilities, and expertise in real-world study design. Companies that master the generation and interpretation of high-quality RWE will gain a significant advantage in navigating the evolving regulatory trial pipeline and demonstrating the true value of their products.

Patients stand to benefit from this evolution through faster access to therapies for rare diseases, more tailored treatment recommendations, and a more complete picture of potential benefits and risks. The ability to monitor drug performance in real-world settings also allows for quicker identification of safety signals or unexpected benefits, leading to more responsive regulatory actions. This iterative feedback loop between clinical practice and regulatory oversight ultimately strengthens the evidence base supporting treatment decisions.

Still, clinicians must remain critical consumers of RWE. The observational nature of much real-world data means that confounding and bias are inherent challenges, even with sophisticated statistical adjustments. Understanding the strengths and limitations of different RWE studies, much like understanding trial design, is important for integrating these insights responsibly into patient care. A comprehensive resource like the Oxford Handbook of General Practice can be invaluable for navigating these complex evidence streams.

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