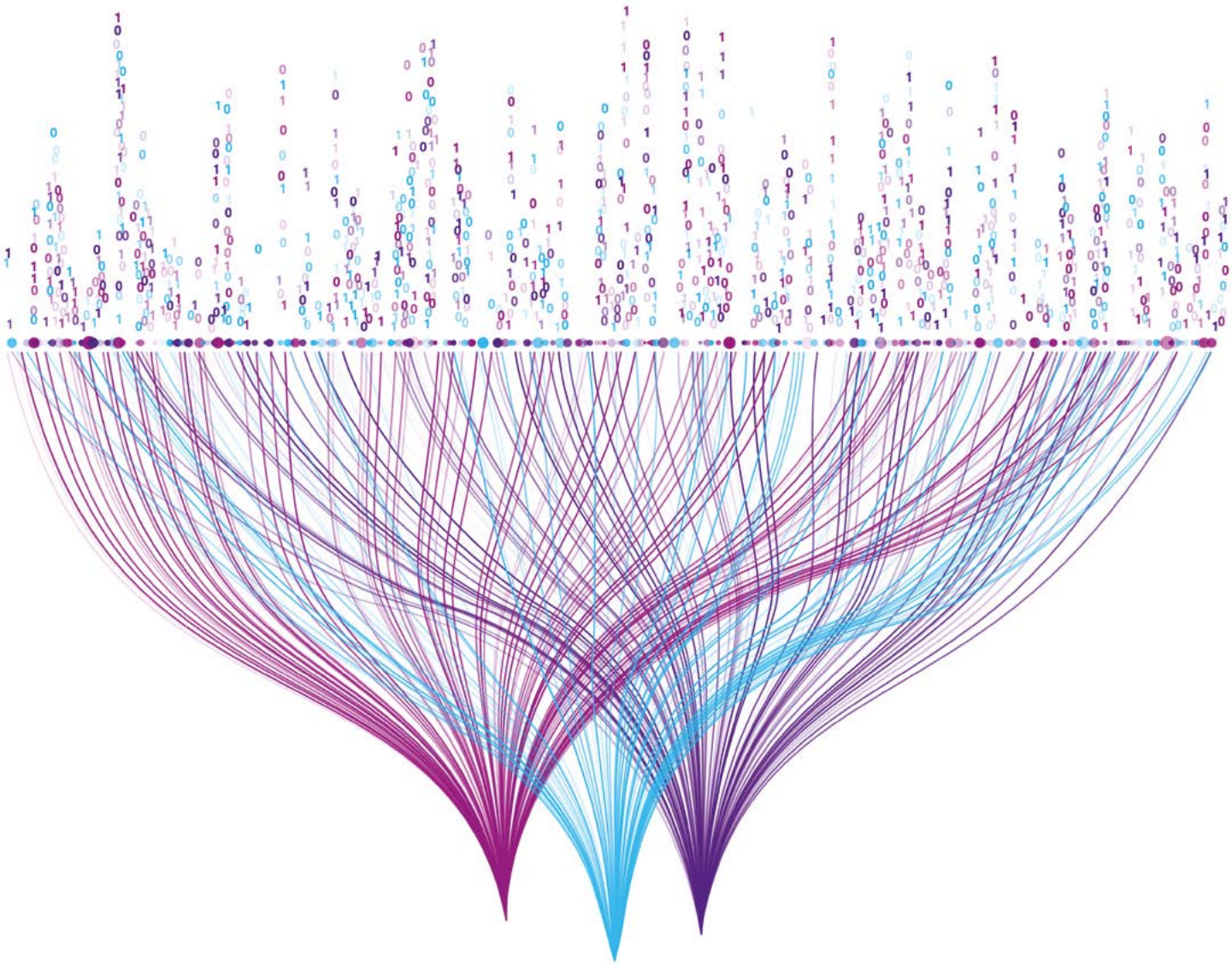

FEATURE

The expanding role of real-world evidence in the regulatory environment

While real-world evidence has established value with health technology assessment bodies and payers, it is now gaining traction within the healthcare regulatory community

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Randomised controlled trials (RCTs) have traditionally been considered the gold standard for drug approvals. However, their limited generalisability, increasing and overly controlled complexity, coupled with limited patient populations for orphan drugs and rare diseases, has forced regulatory agencies to look for alternative or complementary data sources for the evaluation of new novel medicines. Real-world data (RWD) – data derived from a variety of sources from patients, caregivers, or healthcare workers, collected prospectively or retrospectively, via pragmatic controlled trials, registries, administrative data, health surveys, and electronic health records (EHRs) – are increasingly playing a role in pre- and post-marketing authorisation approval.

Real-world evidence (RWE) is not a new phenomenon for regulatory affairs professionals because pharmacovigilance has historically relied on RWD sets from science-based sources such as laboratories, medical imaging, genomics, and proteomics, as well as EHRs, claims

data, and surveys. Examples are the US FDA's post-marketing surveillance system developed in 2008, known as Sentinel, which uses diverse healthcare data such as EHRs, claims, and registries. The EU-ADR is another database designed for the early detection of adverse drug reactions by data-mining and applying computational techniques from medical databases from four European countries.

The expanding volume and complexity of RWD being captured across multiple settings and devices offers an unsurpassed opportunity to better understand diseases, new therapeutic interventions, and patient outcomes. There has been a noticeable increase in the attention given to RWD use beyond approval, with many health technology assessment (HTA) bodies giving weight to RWE in their evaluations. However, regulatory agencies have been slow to consider RWE beyond its traditional use of providing insight into the safety and efficacy of an intervention. That is beginning to change.

The availability of new, rich data that can help provide a true picture of a treatment's value cannot be ignored. However, the increasing availability of RWE from multiple, disparate datasets, advances in cutting-edge technology platforms, and disruption from new technology companies are presenting regulators with new challenges as they seek to understand the acceptability of these data in the regulatory context.

Utilising real-world evidence

The 21st Century Cures Act (Cures Act) in the US mandated the FDA to explore the utility of RWD and RWE for enabling the acceleration of medical product development in order to bring new innovations more rapidly to patients who need them. The FDA has consequently established the Real-World Evidence Program to ensure further rigorous evaluation and expansion of the potential use of RWE to support the approval of new indications, or to help support or satisfy post-approval study requirements for marketed drugs and biologics. Under the auspices of the 2018 Real-World Evidence Framework, the FDA has issued the first draft RWE Guidance for Drugs/Biologics in May 2019 titled "Submitting documents utilizing real-world data and real-world evidence to FDA for drugs and biologics. Guidance for industry".[1] The primary goal of this guidance is to help the FDA internally track investigational new drugs, new drug applications, and biologics license applications which include RWE, in order to help the agency fully understand the scope and use of RWE submitted by companies in support of the requested regulatory decisions regarding safety and effectiveness. To date, the FDA has allowed the use of RWE to support product effectiveness, and made regulatory decisions based on RWE, in very specific and limited cases – predominately in rare diseases, vaccines, and oncology.

Europe is also seeing significant progress towards the use of RWE. Over the past five years, the European Medicines Agency (EMA) has made major steps in the path towards determining when and how in the product lifecycle evidence derived from RWD may be acceptable for regulatory decision making. Specifically, the Heads of Medicines Agencies (HMA) and the EMA formed the HMA/EMA Joint Big Data Task Force to describe the big data landscape from a regulatory perspective in order to ensure the EU regulatory system has the capability and capacity to guide, analyse, and interpret these data. One of the mandates of the task force is to generate a list of recommendations and evaluate the usefulness of big data in the regulatory setting. The EMA also addresses RWD in its "Regulatory science to 2025 strategic reflection"[2], where it outlines specific goals to promote the use of high quality RWD in decision making, develop network competence and specialist collaborations to engage with big data, diversify and integrate the provision of regulatory advice along the entire development continuum, and further develop external engagement and communications, particularly with HTAs and payers, regarding therapeutic context and patient perspective, among others. Individual countries within Europe vary in the degree in which they consider RWE, most still giving more weight to its use in reimbursement and access decisions, with regulatory decisions still predominantly relying on clinical data. It is clear, however, that there is acknowledgement that RWE holds value and regulatory agencies are paying attention and, at the very least, evaluating its merit.

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In China, RWE has limited applicability at present. However, the National Medical Products Administration's (NMPA) Centre for Drug Evaluation (CDE) is beginning to explore uses of RWE to provide supporting evidence for product registration and label expansion, as well as assess the efficacy and safety of products following approval. In 2019, the CDE published a draft guidance on "Key considerations in using real-world evidence to support drug development" to help companies understand how RWE, albeit limitedly, can be used in drug development and regulatory decisions. Any use of RWE for the purpose of product registration requires adequate communication in advance with regulatory authorities to ensure alignment on the study objectives and methodology. In addition, the CDE proposes a standard and quality assessment for RWD, with quality mainly assessed by its relevance and reliability, which requires RWD to be complete, accurate, representative, etc. Data standards ensure the submitted data are predictable and consistent in order to generate meaningful evidence. The draft guidance document does outline specific real-world study designs, including pragmatic clinical trials, single-arm studies, and observational research, and identifies associated weaknesses. However, the CDE does not rule out the use of RWD in the generation of evidence to support

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regulatory decisions and, indeed, there are precedents for its use in special cases, such as oncology and rare diseases.

Overcoming obstacles

Despite the increasing attention by regulators on RWD, a number of obstacles remain before its potential can be seamlessly integrated into the regulatory process. These obstacles have been broadly defined into two groups:[3]

- Technical/operational readiness, which relates to factors like extent of EHR coverage, use of structured data, interoperability of databases, and data quality
- Data governance readiness, which addresses legal issues impeding secondary data analysis, including data privacy concerns, level of consent required, and clarity on who has legal access to health data for research purposes.
- One of the biggest bottlenecks remains – that RWD, even of good quality, do not necessarily translate into credible evidence in the absence of adequate statistical methods to extract, analyse, and interpret them.[3]

Despite these challenges, the use of RWD will increase significantly over the coming years. The continuing developments in complex technologies and trial scenarios, as well as the increasing use of single-arm studies, will pose new challenges for regulators, HTA bodies, and the biopharmaceutical industry. How should regulatory affairs professionals respond to this rapidly evolving regulatory and reimbursement landscape?

First, RWD requirements vary depending on unmet need, product or technology, indication, and quality of data available, including comparator data. Therefore, early regulatory and HTA engagement is critical in order to address these issues and align on an acceptable path forward for all stakeholders. Engaging HTAs and payers early along with regulators can significantly add to the probability of success.

Integrated scientific advice (ISA) is a multi-stakeholder process that brings together regulatory advice and HTA/payer advice. Early engagement via ISA is a valuable strategy to refine and evaluate evidence generation plans and align them with regulators and HTA/payer requirements. There has been steady and notable growth of new options over the past half-decade for seeking multi-stakeholder advice. This growth has been largely fuelled by:

- Novel transformational innovations such as advanced therapy medicinal products and gene/cell therapies
- Immuno-oncologic therapies and personalised medicine
- Novel clinical development programmes
- Significant progress towards patient-centred trial design
- New regulatory and reimbursement pathways (eg, adaptive pathways).

Taking a strategic approach to ISA ensures alignment across different internal functional teams on objectives and early agreement on different options for regulatory and HTA success. Most importantly, early discussions with regulators on study design and RWE is critical prior to study conduct and submission to ensure alignment and avoid future pitfalls. There are several different options available for ISA and, therefore, a systematic framework is required to ensure the preferred option that meets the needs of the asset and addresses time-cost trade-offs is chosen.

Data must be of sufficient quality to address key regulatory and HTA/payer concerns to ensure acceptability by these stakeholders. Addressing methodological issues like those outlined above and preparing for increasing standards for the use of RWD will serve manufacturers well as they navigate the disparate needs from different markets and health agencies.

A holistic RWD strategy aligns elements of patient engagement with evidence collection strategies. This integrated approach yields immeasurable benefits as the increased focus on RWD collection encourages increased attention from patient groups, providing value-added services and opportunities for interaction. This is particularly important for rare diseases and complex technologies which require a perspective of a continuum of evidence as "every data point matters" across a product's lifecycle. This shift in paradigm is particularly important in supporting long-term effectiveness and safety.

However, RWD should not be viewed in isolation but should be part of an integrated value and evidence strategy and plan. Companies that can successfully leverage insights from RWD to build a continuous feedback loop for product development and lifecycle strategies will most likely be the leading innovators when it comes to utilising RWD to support product value. A key driver of product success is an end-to-end evidence generation plan that starts with the strategic development of a unique and compelling value proposition and consequent evidence gaps. Thereafter, a systematic assessment of the diverse approaches to data generation, based on the scientific questions being addressed, can help determine the optimum balance of retrospective (EHRs, claims, registry data, chart reviews, etc) versus prospective (cross-sectional studies, registries, clinical and pragmatic trials, etc) data generation.

In low prevalence diseases or complex technologies, natural history data from multiple markets will be foundational for supporting registration and HTA/payer assessments. These studies should aim to leverage the efficiencies of secondary data collected but also incorporate opportunities for supplemental data collection to enhance patient-reported outcomes and health economics evidence related to burden of disease and unmet need. Innovative programmatic approaches to study design and execution such as platform protocols and modularised case report

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forms can be leveraged to improve operational efficiency for a tailored data acquisition strategy.

RWD can be used creatively to bridge evidence gaps for approval or used post-approval to support label expansion or for protecting pricing and reimbursement during renegotiations. Post-approval, RWD has been successfully leveraged to address gaps in the medical narrative of the product, support local and regional pricing and tendering negotiations, and bring to life the patient voice through their treatment preferences and journey.

Evolution of data

The regulatory and reimbursement environment is evolving rapidly as it relates to the acceptability of RWD. Yet transformative technologies are evolving at an even greater rate. Connectivity brought about by the digitisation of healthcare can amplify the patient voice and the type of data collected. Multiple new innovations are driving this growth. Data is the next frontier and, with the increasing availability of multiple and disparate datasets coupled with advances in cutting-edge technology platforms, big data will fundamentally change the future regulatory landscape.

With new technology players collecting, aggregating, and accessing healthcare data, and new deep technology rapidly transforming digital technologies such as artificial intelligence, machine learning, and distributed ledger technologies (blockchain), regulatory authorities will need to adapt quickly, and regulatory professionals will need to acquire new competencies and leadership capabilities to help lead companies through their data and digital transformations.

In the not-too-distant future, new innovations in patient care are likely to consist of drug-device-digital combinations, challenging conventional regulatory pathways. Given that biometric technology is included in 100% of smartphone shipments by 2020 and that health-related posts on social media have become a rapid means to assess patient views regarding treatment, physicians, and health, regulatory professionals must seek strategic ways to maximise the value of RWD and require platforms to accelerate the adoption of RWD across the full spectrum of users. ■

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