

White Paper

RWE: FROM “NICE TO HAVE” TO “MUST HAVE”

*Are you ready to meet healthcare stakeholders’
ever-increasing evidence demands?*

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RWE HAS COME OF AGE

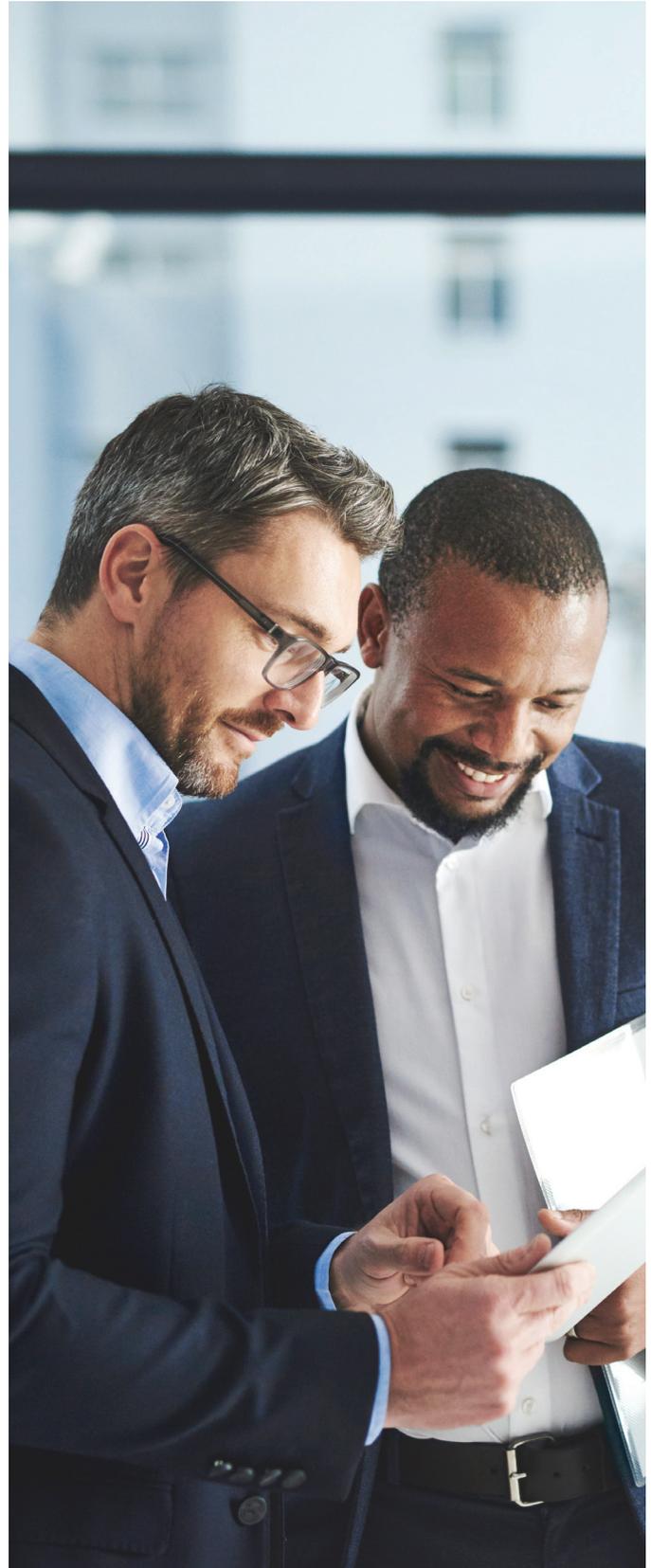


Traditionally, Real-World Evidence (RWE) has had its place in satisfying post-launch regulatory requirements principally related to drug safety. RWE has since been expanding

well beyond its beginnings in pharmacovigilance and has found widespread acceptance for a range of use cases with different healthcare stakeholders, including regulators, Health Technology Assessment (HTA) bodies, payers and Healthcare Professionals (HCPs). Initial scepticism and uncertainty about the robustness of real-world data, and the analytical methodologies used to derive RWE, have given way to the appreciation by those stakeholders of the value RWE brings in addressing their needs. This expansion has gone hand in hand with the digitisation of healthcare combined with innovation in technology and analytics.

In this white paper, we will review the landscape of use cases for RWE among different healthcare stakeholders with a focus on Europe, while highlighting variations and limitations in RWE acceptance. We will further look at trends that are shaping this dynamic picture and how they might play out over the medium term. Finally, we will draw out implications for pharmaceutical companies of how to embrace this new world.

Although not a focus for this white paper pharmaceutical companies' internal use of RWE is increasing. They are using it to inform strategic and operational decisions, for example target product profile (TPP) development, clinical trial design, patient recruitment, financial forecasting or commercial resource allocation.



EXPANDING USE OF RWE

The march of RWE has been relentless. Today, we find a wide range of use cases for RWE along the entire product lifecycle, spanning both the pre- and post-launch phase. Applications of RWE have also moved downstream from their original regulatory focus, to address the specific needs of different healthcare stakeholders, including payers and HCPs (see exhibit 1).

The sheer scale and pace of medical innovation is creating increasing complexity and uncertainty for healthcare stakeholders and is a major driver behind the expanding use of RWE. For example, regulators and payers struggle with understanding clinical value supported by limited evidence packages associated with an accelerated or early approval, where outcomes may have been extrapolated, e.g., overall survival (OS) from progression-free survival (PFS) for oncology products, or where comparators are missing, e.g., in single arm trials. At the same time, HCPs are overwhelmed by the proliferation of treatment options and the fragmentation of patient

populations into smaller and smaller sub-segments, which making it increasingly challenging for HCPs to accurately identify and characterise patients and then match them with the optimal treatment option. Against this backdrop, RWE has an invaluable role to play in eliminating uncertainty and guiding healthcare stakeholders' decisions across the board.

To illustrate the breadth of today's RWE applications, we are highlighting three compelling use cases with different healthcare stakeholders at different stages in the product lifecycle:

1. Facilitated regulatory pathways

Unprecedented levels of innovation are yielding promising new treatment options for areas of high unmet need. Understandably, patients and HCPs alike are demanding earlier access to such novel treatments. As a consequence, regulators are faced with the challenge of accelerating approval in cases of high unmet need, while still ensuring the safety

EXHIBIT 1: STAKEHOLDER USE CASE LANDSCAPE

	RWE USE CASE	REGULATOR (EMA)	HTA/PAYER	HCP
Pre-launch	Characterise disease burden, current treatment pattern and disease epidemiology in order todescribe disease natural history	...quantify unmet need; size of target patient population	...show where my product fits current standard of care ...identify undiagnosed patients ...show medical unmet needs
	Determine the cost of current treatments and healthcare burden of my target disease in order to...		...model budget impact and cost effectiveness to demonstrate value	
Post launch	Show that my drug is as clinically effective in the real-world setting as shown in RCTs in order to...	...meet conditional approval requirements	...demonstrate RW benefit vs local comparators and/or broader population	...demonstrate RW benefit: Overall, vs. relevant local comparator(s), in relevant sub-population(s)
	Demonstrate that my drug is used in a way that aligns with the label in order to...	...satisfy post marketing regulatory commitments	...maintain optimal market access and (re) negotiate pricing	...inform revision of clinical guidelines
	Prove the safety of my drug in the real-world setting in order to...	Traditional RWE use case	...support design and use of novel value based payment mechanisms	...reassure HCPs in product use
	Use PROs to demonstrate that therapy improves HR-QoL in a real-world setting in order to...			...generate compelling patient value messages
Line extension	Prove the effectiveness and acceptability of my drug in un-mandated patient groups in order to...	...support a line extension	...support case for broader access	...reassure HCPs in using product in new patient population

and efficacy of new drugs. To this end, they have created facilitated regulatory pathways, such as breakthrough designation, accelerated approval and adaptive licensing, which accept a higher degree of uncertainty at the time of regulatory approval, but therefore require extensive post-authorisation data to validate the initial assessment.

RWE, from both retrospective and prospective sources, is a critical enabler for these alternative regulatory pathways. The distinctive feature of RWE, i.e. capturing patient-level observations in routine clinical practice, make it the evidence of choice for regulators seeking to confirm a drug's safety and effectiveness. For example, the EMA final report on the adaptive pathway pilot programme highlights that *"all of the 18 proposals accepted in stage II of the pilot included plans for the use of real-world data to supplement randomised clinical trials that went beyond the traditional use of a registry to investigate safety aspects"*. The innovative use of electronic medical records (EMRs), especially when those are linked across data sources and settings of care, holds particular promise in this context¹.

2. Early engagement with market access stakeholders

RWE utility is also expanding into early engagement with HTA bodies and payers. As our proprietary IQVIA HTA Accelerator data show, RWE now plays an increasingly important role in initial submissions:

- » In the UK, the share of initial submissions to the National Institute for Health and Clinical Excellence (NICE) that include RWE has steadily increased over the past three years, from 9% in 2015, 22% in 2016 to 37% in 2017
- » In France, about 25% of initial submissions to the Haute Autorité de Santé (HAS) now include RWE
- » In 2017, even Germany, which is traditionally sceptical, has seen one initial G-BA submission that included RWE, which in turn was awarded a positive assessment

Crucially, our analysis also suggests an association between RWE inclusion and more favourable HTA recommendations. In 2017, only 12% of recommendations in the UK were negative for initial submissions that included RWE, compared to 23% for those without. Whereas in France, in 2016 and 2017 of all positive HAS decisions for initial submissions without RWE 11% had restrictions imposed vs. none for those submissions that included RWE.

"In 2017, only 12% of initial submissions to NICE that included RWE received a negative recommendation vs. 23% for those without."

During this early engagement, RWE has proven to be particularly useful in addressing uncertainty around the burden of illness, unmet need, the size of target patient populations and clinical value. Notwithstanding variations between countries, which we elaborate on below, today many European HTA agencies provide suggestions for specific RWD sources as well as guidance on their suitability to answer different questions². Equally, payers increasingly acknowledge the value of RWE in reducing uncertainty around value and potential overall cost burden of new therapies.

In one example of market access stakeholders engaging early with RWE, IQVIA worked with one company to drive disease awareness and support the need for novel treatment options in a disease area largely unknown to the payer community. Compelling real-world evidence was generated via a network of 10 hospitals and the pooling of EMR data covering >50,000 patients. This enabled constructive engagement with payers and resulted

in successful HTA submissions. Importantly, engaging payers early - during the design of the evidence generation approach - was critical to ensuring HTA bodies were highly receptive to the RWE being presented.

In another recent example of a novel treatment for breast cancer, a manufacturer engaged early with local HTA bodies to understand likely gaps in the evidence being generated via their global clinical trial programme vs. local HTA requirements. Specifically, in the absence of OS data, the HTA agencies were interested in understanding PFS impact on quality of life (QoL), to determine the value of delayed progression. In addition, the manufacturer learned about expectations for extrapolating OS from PFS data in specific target patient cohorts. Informed by this insight, the manufacturer developed a comprehensive strategy for closing the evidence gap including the prospective collection of RWD, with embedded PROs (patient reported outcomes), as well as setting up a pan-European RWE network via collaborations with relevant data source owners, such as breast cancer registries and specialist cancer centres collecting EMR data.

Aligning early with market access stakeholders on innovative analytical methodologies for evidence generation pays off. This was apparent in the recent case of a now highly successful treatment for haematological malignancies. The product secured accelerated market access in Europe by ensuring buy-in for a novel approach of matched adjusted indirect comparisons based on RWE to demonstrate superior outcomes.

3. *Shaping clinical practice guidelines jointly with healthcare stakeholders*

According to a recent pan-European survey of healthcare stakeholders³, 48% of respondents believe

RWE is “highly likely” or “very highly likely” to improve the development of clinical guidelines, while a further 33% of respondents believe this is ‘likely’.

Again, the value of RWE lies in its derivation from routine clinical practice, thereby overcoming inherent limitations of highly controlled RCTs in terms of representativeness of both real-world patient populations and clinically relevant situations in a real-world setting. This presents an opportunity for manufacturers to engage with healthcare stakeholders via RWE in jointly shaping clinical guidelines.

Examples that have been informed by RWE include European Respiratory Society guidelines for the treatment of Idiopathic Pulmonary Fibrosis (e.g., guidance on anti-acid medications, bilateral vs. single lung transplantation), or treatment guidelines by the European Crohn’s and Colitis Organisation (e.g., long-term use of thiopurine in Crohn’s patients).

Apart from clinical societies, HTA bodies are equally embracing RWE when issuing guidance on clinical practice. For example, in the UK real-world data from the NHS Clinical Practice Research Datalink (CPRD) has been used to confirm the safe use of the MMR vaccine, to inform NICE cancer guidance and to influence the management of hypertension in diabetics.

As healthcare stakeholders are becoming increasingly comfortable with RWE, they better understand where, and how, RWE complements traditional RCT data, observational studies and primary market research, thereby firmly establishing RWE as part of the evidence mix they rely on for guiding their decisions.

GEOGRAPHIC VARIATIONS - TODAY & TOMORROW

For all the traction RWE has been gaining with healthcare stakeholders, its acceptance is by no means uniform and indeed varies considerably between countries. Such geographic differences are particularly pronounced in use cases related to market access, as highlighted in exhibit 2.

At one end of the spectrum, countries most receptive towards RWE, e.g., UK, are willing to consider RWE-derived treatment effects, for example where RCT-generated evidence is limited, e.g. in orphan diseases. At the other end, scepticism over the robustness of RWE for demonstrating treatment effects prevails amongst market access stakeholders, e.g., in Germany or Spain. They continue to look to RCTs for efficacy, while RWE is typically used for epidemiology, patient population sizing, characterising burden of illness or understanding current treatment standards.

It is worth noting that the acceptance of RWE for post-launch re-assessments is consistently more favourable across EU5 countries, relative to initial assessments.

Looking ahead, over the next five years we expect to see market access stakeholders' familiarity with and

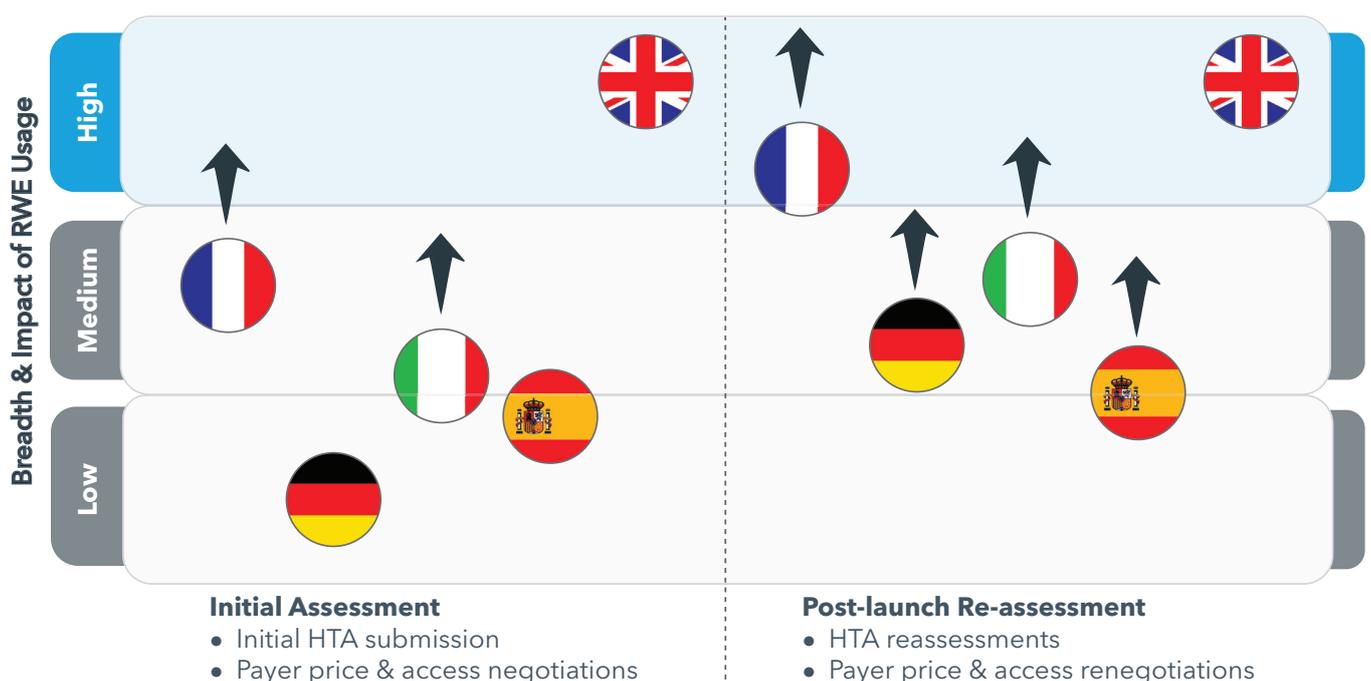
acceptance of RWE continue to grow in both settings and eventually translate into an essential requirement, including in support of treatment effects. A number of harbingers suggest that this trend is well underway.

According to an Italian payer IQVIA interviewed, "several ongoing initiatives will improve the quality of RWE and address existing concerns about its robustness. Consequently, we will see wider scope for RWE to be considered as credible supporting evidence, both clinical and economic, for example in manufacturers' negotiations with AIFA."

Several payers in Spain to whom IQVIA spoke believe that "as post-launch re-assessments will become compulsory and also include pharmacoeconomic evaluations, RWE is going to have more impact. However, this is contingent on improvements in patient data collection, e.g., via disease registries and better electronic medical records, to generate high quality evidence."

In a recent German example, RWE-derived treatment effects played an important role in supporting positive recommendations. A high cost specialty

EXHIBIT 2: VARIATION IN RWE USAGE IN MARKET ACCESS DECISIONS ACROSS EU5



drug was undergoing post-launch re-assessment, as part of the AMNOG process. In its dossier, the manufacturer submitted a re-analysis of pivotal trial data, while during the price negotiations this was further validated with sub-population specific RWD studies using EMR data extracted from a panel of clinics across Germany. The RWD analysis focused on real-world use and comparative outcomes, and it demonstrated positive benefit vs. comparator in each of the three sub-populations included in the product's label. The product was awarded a positive benefit rating, which ensured the continued use of the drug across all indicated populations, and avoided reference pricing. Remarkably, all competitors in this therapy area have subsequently started to generate RWE in support of their products in Germany.

Meanwhile, the use of RWE by market access stakeholders in France is showing signs of becoming ever more formalised, as illustrated by the example

of a crowded and highly competitive neurological indication, for which all recent re-assessments have seen the provision of RWE to support effectiveness and safety claims.

Interestingly, some smaller European countries, such as the Nordics, Netherlands or Portugal have generally been more enthusiastic than their bigger neighbours in embracing RWE, and over the next five years we foresee RWE being included as a "must have" in the evidence mix to inform their pricing and market access decisions.

Finally, looking beyond national market access, in the medium term we also expect RWE to become increasingly critical for achieving sub-national access across Europe, for example as an enabler for indication-specific or value-based contracting with regional or local budget holders, as relevant RWD infrastructure is being built (e.g., The Collaboration for Oncology Data in Europe (CODE⁴)).

CONCLUSIONS

With RWE firmly established as part of the evidence mix, and its role in informing healthcare stakeholders' decisions further expanding, pharmaceutical companies need to take a strategic approach to RWE. This requires systematic, coordinated planning, with anticipation of future needs, while ensuring organisational agility and readiness, and while committing to longer-term RWE investment plans:

1. Integrated evidence strategy

- a. Take a broad view of opportunities for RWE, considering a wide range of potential use cases, across all healthcare stakeholder types
- b. Gain a thorough understanding of stakeholder needs, current and future, which has been validated externally
- c. Systematically plan evidence generation and use across the product lifecycle, while anticipating future requirements of the different functions within the company - starting in the early development phase - to be prepared, given the lead time for generating evidence

2. Organisational agility and readiness

- a. Ensure access to critical capabilities, including RWD, technology and skilled talent - either built in-house or via partnerships
- b. Put organisational enablers in place, for example, fit-for-purpose processes, effective governance and the right mind-set for using RWE
- c. Secure senior executive sponsorship for the RWE strategy

3. Longer-term commitment to RWE investment

- a. Develop longer-term RWE investment plans, covering both evidence generation and ensuring organisational readiness
- b. Incorporate RWE investment requirements into budgets, with multi-year commitments

4. Driving RoI from RWE investments

- a. Start with focussing on high priority TAs
- b. Move beyond study-based mind-set
- c. Capture synergies by consolidating evidence generation plans at the franchise/TA level and avoid duplication due to uncoordinated, individual initiatives
- d. Enable the streamlined generation, and appropriate re-use, of evidence, e.g., via evidence platforms, as well as its internal dissemination, e.g., via portals and effective sharing mechanisms
- e. Communicate RWE effectively to healthcare stakeholders, within applicable legal frameworks

RWE has come of age and is here to stay. As healthcare stakeholders increasingly accept, and indeed expect, RWE as part of the information to guide their decisions, it is imperative for pharmaceutical companies to embrace RWE strategically in evidence planning, generation and communication.

By approaching RWE in a smart way and investing wisely, pharmaceutical companies can contain incremental spend requirements as they realise extensive efficiencies and synergies, while driving substantial returns from their RWE investments.

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Markus has over 20 years of experience in life sciences, most recently as VP Real-World & Analytics Solutions, focussing on helping client with RWE strategies and building the enabling infrastructure, such as evidence platforms. Prior experience spans a broad range of commercial topics, including launch readiness, go-to-market models, brand & commercial strategies, organisational design & transformation. Markus holds a PhD in pharmaceutical chemistry.



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