PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

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We outline our vision that by 2025 the use of real-world evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

Real-world data (RWD) and real-world evidence (RWE) are already used in the regulation of the development, authorization, and supervision of medicines in the European Union. Their place in safety monitoring and disease epidemiology are well-established while their evidentiary value for additional use cases, notably for demonstrating efficacy, requires further evaluation.[1] During the coronavirus disease 2019 (COVID-19) pandemic, RWE rapidly provided impactful evidence on drug safety, vaccine safety, and effectiveness and we were reminded of the importance of robust study methods and transparency.[2] Our vision, anchored in the European Medicines Regulatory Network (EMRN) strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases.[3] Delivering this vision will support the development and use of better medicines for patients.

In December 2018, the US Food and Drug Administration (FDA) published its framework for RWE underpinned by three pillars: whether RWD are fit for use, whether the study design can provide adequate evidence, and whether the study conduct meets regulatory requirements.[4] In 2019 in the European Union, we published the OPTIMAL framework for RWE also consisting of three pillars: operational, technical, and methodological.[5] More recently, the EU approach places RWE in the wider context of big data and is guided by the priority recommendations of the Big Data Task Force. These recommendations are being implemented through the Big Data Steering Group and the second multi-annual work plan was published in August 2021.[6] **Figure 1** represents the workplan with its 11 workstreams which will deliver our vision for RWE by 2025. The workplan places emphasis on collaboration across stakeholders and with international

regulatory partners. This work also needs to be seen in the wider EU policy context, most notably the European Commission's plans for a European Health Data Space.[7]

Acknowledging different frameworks to conceptualize the challenges and opportunities of RWE, we believe the two main priorities for the European Union are to enable its use and establish its value for regulatory decision making. The EMRN is working to deliver on both priorities through a collaborative approach where we leverage the best that different stakeholders can bring, and where those stakeholders can complement the central role of industry in generating evidence.

ENABLING USE

To enable use, we are working on multiple fronts with our stakeholders, including patients, healthcare professionals, industry, regulatory and public health agencies, health technology assessment bodies, payers, and academia. We are initiating work to establish a data quality framework, not just for RWD but for all data used in regulatory decision making. We are striving to improve the discoverability (findability) of RWD through agreement of metadata for RWD and through a public catalogue of RWD sources[8] that builds on the early work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Guide on Methodological Standards in Pharmacoepidemiology,[9] extensively updated in 2021, is the core of our efforts to drive up the standards of study methods for RWE, and this is complemented by recently published guidance on conducting studies based on patient registries.[10]

The European Medicines Agency (EMA) and some national medicines agencies

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Figure 1 Big Data Steering Group workplan to 2023. Eleven workstreams to progress the real-world evidence (RWE) vision.[5]

have, individually, been investing in access to RWD. Building on this experience, in 2021, the EMRN initiated plans to create an EU-wide distributed network of RWD named the Data Analytics and Real World Interrogation Network (DARWIN EU).[11] DARWIN EU launches in early 2022 with the establishment of its coordination center to on-board data partners and to drive the conduct of studies requested by medicines regulators (and in time requested by other stakeholders). The establishment phase of DARWIN EU has been funded by the European Commission through EU4Health and the long-term sustainability will come through industry fees charged by the EMA. We will work collaboratively to ensure that DARWIN EU delivers benefits for stakeholders. We will pilot regulatory use cases across the lifecycle of medicines, from disease epidemiology that supports decisions on the development of products, to safety studies for products on the market allowing rapid and robust evaluation of safety signals. This will bring benefits across stakeholders, supporting industry's research on its products, supporting Health Technology Assessment and payer decisions, and ultimately facilitating access for patients to new and optimally used products.

ESTABLISHING VALUE

Enabling access to RWD provides the foundation for conducting high quality studies that generate evidence for regulatory decision making. However, the place of RWE in that decision making, its evidentiary value, remains a subject of debate.[12] This is particularly true in the demonstration of efficacy when a product is first approved compared with further explorations of established effects once the medicine is approved. We believe that the binary discussion between clinical trials and RWE is unhelpful as each approach brings its own strengths and weaknesses. Whereas the randomized clinical trial remains the gold standard for of the initial demonstration of efficacy, there is a place for RWE through the different regulatory touchpoints of a medicine's lifecycle. But the evidentiary value, particularly compared with clinical trial results, is not equal across these touchpoints.

We are working on multiple fronts to establish the evidentiary value of RWE. We seek to understand when a randomized clinical trial and when RWE is best placed to provide robust, decision-ready evidence. Put differently, we seek to embrace a complementary evidence approach rather than seeing the two as being in opposition.

We see learning from what we do as a central part of this work and the review in this edition, showing 40% of marketing authorization applications to the EMA in 2018–2019 contained RWE, is an important example of this.[1] In November 2021, we held a "learnings initiative" workshop, that brought together stakeholders to review efforts to learn about RWE and to identify processes that could be used to ensure our learning is comprehensive and continuous to support the improvement of regulatory practice.[13] We are integrating the findings of that workshop into our work planning for the coming years. We are also collaborating with research funders to ensure independent, original research is conducted into the applicability of RWE and on study methods, and we welcome recent research calls from the European Commission that explicitly recognize the link of RWE in general and DARWIN EU specifically to regulatory decision making.[14]

Finally, it is critical that the regulator, both in facilitator and gate-keeper role, has the skills and knowledge to advise, to analyze, and to judge RWE. The EMRN is investing to upskill our workforce and this is being

delivered through targeted recruitment, through setting up a range of dedicated training programs and through sharing of good practice in clusters of excellence.

CONCLUSION

Our vision is that by 2025 the use of RWE will have been enabled and its value will have been established across the spectrum of regulatory use cases. We are committed to working with stakeholders to deliver this vision and in turn to support the development and use of better medicines for patients.

CONFLICT OF INTEREST
The authors declared no competing interests for this work.

DISCLAIMER
The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies with which the authors are employed.

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