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Short communication

Regulatory use of Real-World Data and Real-World Evidence

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Introduction

Real-world data (RWD) are routinely collected data on patient health status and the delivery of health care, generated outside the controlled environment of randomized clinical trials. When these data are systematically analysed, they can generate real-world evidence (RWE), meaning clinical evidence on the use, effectiveness and safety of medicinal products in routine practice (Dang, 2023; FDA, 2018). The increasing digitalization of health care, use of electronic health records, patient registries, claims databases, mobile applications and patient-reported information has substantially expanded the amount of data available for regulatory and public-health evaluation.

Although randomized controlled trials remain the main standard for demonstrating efficacy, their strict inclusion and exclusion criteria may limit generalizability to broader patient populations. RWE can therefore complement clinical trial evidence by capturing outcomes in older patients, patients with comorbidities, users of concomitant therapies and populations followed for longer periods. This is particularly important in oncology, rare diseases and post-authorization safety monitoring, where conventional trial designs may be difficult, expensive or ethically challenging (Dagenais et al., 2022).

Sources and value of RWD

The most established sources of RWD are electronic health records and structured patient registries. Electronic health records provide longitudinal information on diagnoses, laboratory results, treatments, outcomes and medication use, while registries allow standardized collection of information on a specific disease, product or population. These sources can support epidemiological research, recruitment of patients into clinical trials, external comparator arms and long-term monitoring of effectiveness and safety (EMA, 2021; Hoque et al., 2017).

Regulatory use in the European Union and the United States

In the United States, the Food and Drug Administration (FDA) has taken a proactive approach by establishing a framework for the use of RWE in regulatory decision-making and by issuing guidance documents on data standards, registries and study design. The Sentinel Initiative also illustrates the use of large-scale distributed data networks for active safety surveillance of medical products. These activities have made RWD and RWE increasingly visible in submissions intended to support new indications, safety evaluations and post-marketing requirements (FDA, 2018; FDA, 2021; FDA, 2023).

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In the European Union, the European Medicines Agency (EMA) has focused on strengthening the regulatory data infrastructure and methodological capacity for using RWE. Important initiatives include the guideline on registry-based studies, the European medicines regulatory network strategy to 2025, and DARWIN EU, a federated data network intended to provide timely and reliable evidence for EMA scientific committees and national competent authorities. In practice, EU use of RWE has been especially prominent in post-authorization monitoring, disease characterization and safety questions, while its use as pivotal evidence for marketing authorization remains more selective (Arlett et al., 2022; EMA, 2021; EMA, 2024).

A comparison of these approaches indicates that both regions recognize the regulatory value of RWE, but they emphasize different mechanisms. The FDA has issued more direct guidance for sponsors on submitting RWD-based evidence, whereas EMA has invested strongly in networks, common data models and committee-level evidence generation. These differences are complementary rather than contradictory: both approaches seek to improve the quality, transparency and reproducibility of evidence used in medicines regulation.

Challenges and relevance for North Macedonia

The main regulatory challenges are not related only to access to data, but also to confidence in the data and the methods used to analyse them. For RWE to influence regulatory decisions, data sources must be well described, variables must be clearly defined, and the study design must be able to answer the regulatory question. Privacy protection, interoperability of health databases and the ability to audit data provenance are equally important. Without these conditions, large data volumes may produce weak evidence rather than better decisions.

The experiences of the EU and the United States are relevant for countries outside these systems, including the Republic of North Macedonia. Development of interoperable health data systems, disease registries and methodological standards could improve pharmacovigilance, support evidence-based reimbursement decisions and gradually increase regulatory readiness to evaluate RWE in marketing authorization or variation procedures. Alignment with international regulatory trends may also facilitate faster access to safe and effective medicines, especially in therapeutic areas where traditional evidence is limited.

Conclusion

RWD and RWE are becoming important components of modern medicines regulation. They do not replace randomized clinical trials, but they can strengthen regulatory decision-making by providing evidence from routine clinical practice, supporting clinical trial design, enabling external comparators and improving post-authorization monitoring. Their successful use requires high-quality data, transparent methods and close collaboration between regulators, academia, health-care institutions and industry. For North Macedonia, gradual adoption of these principles could provide a practical pathway toward stronger health-data monitoring and more evidence-based regulatory decisions.

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