Final Concept Paper

E23: Considerations for the Use of Real-World Evidence (RWE) to Inform Regulatory Decision Making with a focus on Effectiveness of Medicines
Dated 22 October 2025

Endorsed by the Management Committee on 12 November 2025

1. Type of Harmonisation Action Proposed

With reference to the concept paper outline endorsed by the ICH Assembly in May 2025, the development of a new harmonised Guideline is recommended.

2. Background to the Proposal and Statement of the Perceived Problem

Background to the proposal

Over the last several years, whilst an increasing proportion of regulatory submissions involve real-world evidence (RWE), several studies attempted to measure the frequency and extent of real-world data (RWD) and RWE use in decision-making processes and ultimately medicine approvals (1-6). However, various definitions and the application of diverse methodologies across these studies have led to different estimates of the number of regulatory submissions that included RWE. Although existing definitions from regulators, learned societies, and other organisations, share similarities, the terms RWD and RWE are often used inconsistently and interchangeably (7-10).

In 2022, the International Coalition of Medicines Regulatory Authorities (ICMRA) pledged to foster global efforts to address these challenges (11). Subsequently in June 2024, an ICH Reflection Paper led by the European Commission (EC)/Europe, Health Canada, and the US-FDA outlining a strategy towards harmonisation was endorsed by the ICH Assembly (12). The reflection paper proposed a stepwise approach, with a first ICH guideline focusing on RWD and RWE terminologies, metadata, and assessment principles. It will build on the foundation established by ICH M14 (13), which focuses on the use of RWD for safety assessment, while this new guideline will complement those principles to address effectiveness of medicines, encompassing drugs, vaccines, and other biological products.

Statement of the Perceived Problem

This variability in definitions, as well as the lack of harmonised principles for regulatory assessment of RWE, leads to various challenges. One major challenge is that it hinders a clear understanding of how and when RWD and RWE may be used to support regulatory decision-making, resulting in:

- Potential misalignment among regulators, industry, academia, and other interested parties regarding expectations for the use and tracking of RWD and RWE.
- Complicated efforts among regulators to apply consistent approaches to the assessment of RWD and RWE in regulatory submissions.

3. Issues to be Resolved and Expected Deliverables

Issues to be Resolved

Inconsistent Definitions of RWD and RWE Across Jurisdictions

The need to establish clear, precise, and consistent definitions of RWD and RWE across regulatory bodies is crucial. This will ensure a common understanding of what constitutes RWD and RWE (e.g., the types and methods of data collection, specific contexts), thereby facilitating more harmonised regulatory processes. These definitions will help reduce discrepancies in how RWE is interpreted, evaluated, and used in the assessment, ensuring that all parties are aligned in their approach with regard to RWD and RWE.

Need for Better Characterisation of RWD

Creating a core list of metadata is essential to better characterise RWD and improve their findability, accessibility, interoperability, and reusability as per FAIR (Findability, Accessibility, Interoperability, and Reusability) principles (14). For example, metadata can define the source, location, variables, format, context, and operational aspects related to data collection, storage, cleaning, linkage, validation, and access/sharing. These aspects can provide regulators with the necessary information to evaluate the reliability of the RWD, enabling more informed and consistent regulatory decision-making per regional laws, ethical considerations, and the applicable regulatory requirement(s).

Lack of Convergence of General Principles for Assessment of RWD and RWE, Especially When RWE Is Used to Support Medicines' Effectiveness

As an initial step, the guideline will address important aspects related to regulatory assessment of RWD and RWE, such as data provenance, collection methods, aggregation, transportability, quality, access, governance, as well as feasibility considerations and methodological aspects (e.g., design components). Convergence on these general principles will help ensure that RWD are reliable, relevant, and RWE is assessed consistently across different regulatory jurisdictions.

Expected Deliverables

The level of information to be included in the guideline is expected to be a mix of detailed technical guidance (for a and b) and high-level principles (for c):

a) Definitions of RWD and RWE;
b) Core list of metadata;
c) General principles for assessment of RWD/RWE for regulatory purposes with a focus on effectiveness of medicines.

4. Planning

Type of Expert Working Group

Development of this guideline requires experts from regulatory agencies, industry, and observers with experience in generating and evaluating RWD and RWE to assess the effectiveness of medicines. Core disciplines include pharmacoepidemiology, biostatistics, RWD curation and standards, and RWE methodologies.

Timeframe of the Project

The guideline development would aim to be completed in approximately three years and a half from the appointment of the EWG, including approximately 24 months to reach *Steps 2a (Final Technical Document)* and *2b (Draft Guideline)*.

5. Impacts of the Project and Post-Hoc Evaluation

Benefits of ICH harmonisation

This guideline will aim to support the development and assessment of medicines throughout their entire lifecycle—from pre-approval to post-market studies—regardless of any particular disease area and patient population.

By aligning expectations among regulators, industry, academia, and other interested parties, it will seek to promote greater efficiency, consistency, and transparency in the generation, application, and assessment of RWE. In addition, the guideline can help facilitate decision-making, address unmet medical needs, and support safe and effective use of medicines. It can also create opportunities for early global interactions to increase a shared understanding on the utilisation of RWE for regulatory purposes.

References

1. Flynn R, Plueschke K, Quinten C, et al. Marketing authorisation applications made to the European Medicines Agency in 2018–2019: What was the contribution of real-world evidence? *Clin Pharmacol Ther.* 2022 Jan;111(1):90–7.
2. Bakker E, Plueschke K, Jonker CJ, Kurz X, Starokozhko V, Mol PGM. Contribution of real-world evidence in European Medicines Agency's regulatory decision making. *Clin Pharmacol Ther.* 2023;113:135–51. doi:10.1002/cpt.2766
3. Purpura CA, Garry EM, Honig N, Case A, Rassen JA. The role of real-world evidence in FDA-approved new drug and biologics license applications. *Clin Pharmacol Ther.* 2022 Jan;111(1):135–44.
4. Eskola SM, Leufkens HGM, Bate A, de Bruin ML, Gardarsdottir H. Use of real-world data and evidence in drug development of medicinal products centrally authorized in Europe in 2018–2019. *Clin Pharmacol Ther.* 2022 Jan;111(1):310–20.
5. Bloomfield-Clagett B, Rahman M, Smith K, Concato J. Use of real-world evidence in neuroscience-related new drug and biologics license applications for novel therapeutics. *Clin Pharmacol Ther.* 2023;114:1002–5. doi:10.1002/cpt.3018
6. Asano J, Sugano H, Murakami H, Noguchi A, Ando Y, Uyama Y. PMDA Perspective on Use of Real-World Data and Real-World Evidence as an External Control: Recent Examples and Considerations. *Clin Pharmacol Ther*. 2025;117(4):910-919. doi: 10.1002/cpt.3540. Epub 2025 Jan 3
7. Concato J, Stein P, Dal Pan GJ, Ball R, Corrigan-Curay J. Randomized, observational, interventional, and real-world—what's in a name? *Pharmacoepidemiol Drug Saf.* 2020;29:1514–7. doi:10.1002/pds.5123
8. Concato J, Corrigan-Curay J. Real-world evidence—where are we now? *N Engl J Med.* 2022 May 5;386(18):1680–2.
9. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). *ENCePP Guide on Methodological Standards in Pharmacoepidemiology.* Rev. 11. July 2023. Chapter 15.6.3. Available from: https://encepp.europa.eu/document/download/f6e403a6-8033-4c22-a5ff-195ba3666299_en?filename=01.ENCePPMethodsGuideRev.11.pdf
10. Rahman M, Dal Pan G, Stein P, et al. When can real-world data generate real-world evidence? *Pharmacoepidemiol Drug Saf.* 2024;33(1):e5715. doi:10.1002/pds.5715
11. International Coalition of Medicines Regulatory Authorities (ICMRA). *Statement on international collaboration to enable real-world evidence (RWE) for regulatory decision-making.* 2022. Available from: https://www.icmra.info/drupal/sites/default/files/2022-07/icmra_statement_on_rwe.pdf
12. International Council for Harmonisation (ICH). *Reflection paper: Pursuing opportunities for harmonisation in using real-world data to generate real-world evidence, with a focus on effectiveness of medicines.* 2024. Available from: https://www.ich.org/page/reflection-papers#7-1
13. International Council for Harmonisation (ICH) M14. *General Principles on Planning, Designing, Analysing, and Reporting of Non-interventional Studies That Utilise Real-World Data for Safety Assessment of Medicine*. Available from: https://www.ich.org/page/multidisciplinary-guidelines#14-1
14. Wilkinson MD, Dumontier M, Aalbersberg I, et al. The FAIR guiding principles for scientific data management and stewardship. *Sci Data.* 2016;3:160018. doi:10.1038/sdata.2016.18