Real-World Evidence in FDA and EMA Regulatory Reviews: Insights on Its Role in Submission Packages and Approvals

HPR82

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Background

- Regulatory approvals from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have traditionally relied on evidence from well-designed and well-conducted randomized controlled trials (RCTs), preferably double-blind and placebo-controlled.
- Real-world evidence (RWE) has recently expanded beyond its initial role in safety monitoring and post-marketing surveillance. Both the FDA and EMA now recognize RWE as a complementary source of evidence for assessing efficacy and safety.[1-6]
- As biopharmaceutical companies increasingly integrate RWE into clinical development, there is growing interest in understanding how these efforts influence regulatory submissions and decisions.

Objective

To assess how real-world data (RWD) and RWE are used in regulatory submissions to the FDA and EMA, and to evaluate their impact on regulatory decisions.

Specific Aims:

- ✓ Review historical regulatory submissions involving RWE.
- ✓ Assess the impact of RWE on regulatory decisions.
- ✓ Provide insights to guide use of RWE in future regulatory submissions.

Methods

Regulatory review and label documents (2009–2023) from FDA and EMA were screened using predefined criteria, and key data were extracted to meet study objectives.

The evaluation process is shown in **(Figure 1)**

Figure 1: Regulatory submission evaluation workflow

Selection of Regulatory Selection

150 submissions containing RWE were selected for broad representation across:

- ✓ FDA and EMA
- ✓ Therapeutic areas
- ✓ Application types (e.g., novel drug vs. label extension)
- ✓ Submission categories (e.g., accelerated, conditional, orphan)

Data Extraction

Data extraction conducted by four reviewers followed a structured framework.

Data extracted:

- ✓ Submission and regulatory pathway
- ✓ Disease/treatment context
- ✓ Clinical data
- ✓ RWD/RWE details
- ✓ Regulatory feedback

Validation and Quality Control

Robust validation ensured data quality through:

- ✓ Standardized terminology
- ✓ Extractors training
- ✓ Second-review verification and reconciliation
- ✓ Spot and automated checks
- ✓ Subject matter expert review

Analysis and Trend Identification

Trend Analysis:

- ✓ Explored RWE use by therapeutic area, pathway, data type, and regulatory response.

Insight Generation:

- ✓ Identified strategies to improve future submissions and highlighted RWE's evolving regulatory impact.

Results

Key Findings:

- RWE use cases span both label extensions (n = 45) and novel drug applications (n = 189; **Figure 2**)
- RWE is used more frequently pre-authorization (n = 183) than post-authorization (n = 51; **Figure 3**)

Figure 2: RWE use by submission type

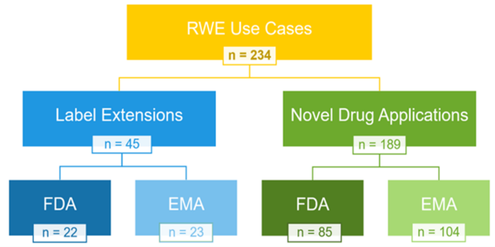
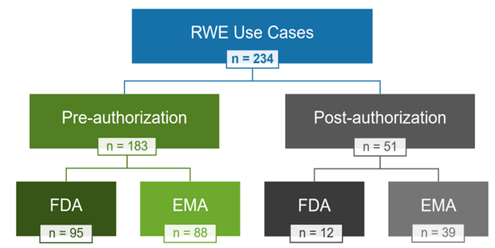


Figure 3: RWE use by regulatory stage

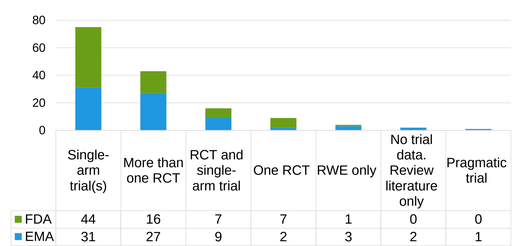


- RWE is often used in fast-track approvals like orphan drugs, accelerated assessment, conditional approval, and priority review **(Table 1)**
- Single-arm trials account for the majority (50%) of submissions. In contrast, submissions relying solely on RWE remain rare (FDA: 1; EMA: 3; **Figure 4**)

Table 1: Overview of the submission pathway

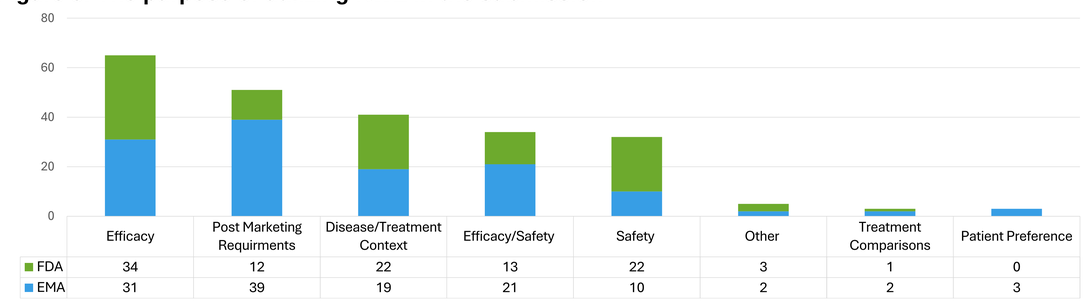
Regulatory Pathway	FDA (N=75)	EMA (N=75)
With orphan designation status	56 (75%)	48 (64%)
Under accelerated assessment	28 (37%)	16 (21%)
Under priority review	60 (80%)	-
Under conditional approval	-	24 (32%)

Figure 4: Main clinical study in the submission



- Treatment effectiveness is the most frequent RWE use case (FDA: 34, EMA: 31), followed closely by post-marketing requirements (FDA: 12, EMA: 39). EMA submissions also includes RWE studies to assess patient preference **(Figure 5)**

Figure 5: The purpose of utilizing RWE in the submission



RWE impact spectrum in regulatory decisions:

Positive Impact on decision (n=164):

- Critical evidence for regulatory decision (n=11)
- Supportive evidence for regulatory decision (n=96)
- Post market commitments/requirements (n=51)
- Limited impact on regulatory decision (n=6)

Not factor into decision (n=70)

- Agency did not accept the submitted RWE (n=3)
- RWE deemed inadequate or insufficient (n=43)
- RWE not used in the regulatory review (n=4)
- No agency comment on RWE (n=20)

Discussions

Use of RWE in Regulatory Submissions:

- RWE was increasingly observed in regulatory submissions from 2019–2023, although interpretation of trends is limited by non-random sampling.
- RWE contributed variably to regulatory decisions, ranging from a critical role to being unused or unacknowledged.

Challenges in Assessing RWE's Regulatory Role:

- Regulatory evaluation is hindered by inconsistent documentation of RWD sources, study design elements, and data quality attributes across submissions.
- Regulatory assessment documents for label extension submissions are often unavailable.

Limitations in Current Review:

- Only approved submissions were assessed. Rejected submissions containing RWD/RWE were not captured.
- The lack of granular clinical data analysis (e.g., effect sizes, trial limitations) limits deeper understanding of RWE's role in the regulatory context.

Future Directions:

- Broaden the review dataset to include both approved and rejected regulatory submissions.
- Enhance the evaluations of RWE submissions by developing a checklist that incorporates study design, methodological rigor, and conformity with regulatory trends.

Conclusion

- RWE plays an increasingly supportive role in regulatory submissions, especially in oncology, rare diseases, and orphan drug applications.
- Emphasizing robust study designs, high-quality data, and regulatory alignment will further enhance its impact.

References

1. *Agency EM. Real-world evidence framework to support EU regulatory decision-making. In: Agency EM, ed2023.*
2. *Agency EM. ICH Reflection paper on proposed international harmonization of real-world evidence terminology and convergence of general principles regarding planning and reporting of studies using real-world data, with a focus on effectiveness of medicines. In:2023.*
3. *FDA. Framework for FDA's real-World Evidence Program. In:2018.*
4. *FDA. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products - Guidance for Industry. In: CDER C, OCE, ed2023.*
5. *FDA. Data Standards for Drug and Biological Product Submissions Containing Real-World Data - Guidance for Industry. In: CDER C, ed2023.*
6. *FDA. Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products - Guidance for Industry. In: CDER C, OCe, ed2023.*

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