IntuitionLabs

INTUITIONLABS / RESEARCH & PRACTICAL GUIDANCE

Regulatory-Grade RWE Platforms for FDA & EMA Submissions

> Build practical AI for pharma and biotech with IntuitionLabs. We help life-science teams turn complex information and workflows into useful software, governed knowledge systems and AI tools.

Published by IntuitionLabs · 2026-04-08 · real-world evidence · real-world data · rwe platforms · fda submissions · ema regulations · pharmacoepidemiology · regulatory affairs

Original article: https://intuitionlabs.ai/articles/real-world-evidence-platforms-fda-ema



In this article

1. Executive Summary
2. Introduction
3. Background: RWD and RWE in Healthcare
4. Definitions and Scope
5. Regulatory Landscape for RWE
6. U.S. FDA Initiatives
7. EMA and European Regulatory Initiatives
8. Global and Multilateral Trends
9. Real-World Data Platforms and Networks
10. Government and Regulatory Data Networks
11. Academic and Consortium Platforms
12. Commercial RWE Platforms
13. Data Standards and Technology
14. Building Regulatory-Grade RWE
15. Data Quality and Fitness-for-Purpose
16. Study Design and Methodology
17. Analytical Implementation
18. Governance and Ethics
19. Data Analysis and Evidence
20. Trends and Statistics on RWE Use
21. Evidence from Case Studies
22. Discussion of Implications and Future Directions
23. Regulatory Implications for Pharma
24. Challenges
25. Future Trends
26. Tables
27. Table 1: Key RWE Data Platforms and Networks
28. Table 2: RWE Use Cases in Regulatory Submissions
29. Conclusion

Executive Summary

The use of **Real-World Evidence (RWE)** – derived from routinely collected **Real-World Data (RWD)** such as electronic health records (EHRs), insurance claims, patient registries, and mobile health data – has surged as a complement and, in some cases, an alternative to conventional randomized controlled trials (RCTs) in drug development and regulatory decision-making. In both the United States and Europe, regulatory agencies (FDA and EMA) have formally embraced RWE under legislative and policy initiatives (e.g. the U.S. 21st Century Cures Act and EMA's Big Data strategy) and launched dedicated programs to build **"regulatory-grade"** RWE platforms and standards (pmc.ncbi.nlm.nih.gov) (www.pharmtech.com).

This report provides a comprehensive analysis of **real-world evidence platforms** tailored for the pharmaceutical industry to generate RWE of sufficient quality and rigor for **FDA and EMA submissions**. We review the historical context and drivers (including statutory mandates and technological advances), survey key global platforms and data networks (government, academic, and commercial), and examine case studies of RWE successfully incorporated into regulatory filings. Technical aspects are explored in depth: data sources, common data models (e.g. OMOP), study designs (cohort studies, external control arms), analytical methods to control bias (propensity scores, target-trial emulations), and informatics tools. We analyze evidentiary standards for "regulatory-grade" RWE – including data quality, transparency, and adherence to good pharmacoepidemiology practices – and discuss how platforms and processes are evolving to meet these requirements. Finally, we discuss implications for stakeholders and the future of RWE, including the integration of AI and global convergence of regulatory frameworks.

Throughout, we draw on the latest research findings and regulatory publications. For instance, a study of FDA-approved labeling expansions from January 2022 through May 2024 found available or potentially relevant RWE for 55 of 218 approvals. Only three were documented in FDA materials; evidence for 52 was found elsewhere. These findings do not establish how often RWE was submitted or used in regulatory decisions (study). Separately, EMA's 2025 annual report described DARWIN EU as covering approximately 180 million European patients (encepp.europa.eu). The original 2021 FDA accelerated approval of Voxzogo (vosoritide) was to improve growth in children aged five and older with achondroplasia and open growth plates, with a required study of final adult height. Nulibry (fosdenopterin) is indicated to reduce mortality risk in patients with molybdenum cofactor deficiency Type A. By synthesizing multiple perspectives – regulatory, industry, methodological, and "on-the-ground" examples – this report offers a **deep, practical guide** for pharma companies and data providers building and using RWE platforms aimed at FDA/EMA submissions.

Introduction

Background: RWD and RWE in Healthcare

Real-World Data (RWD) are broadly defined as data relating to patient health status and/or the delivery of healthcare, collected in routine clinical practice or other non-experimental settings (pmc.ncbi.nlm.nih.gov). Common sources include **electronic health records (EHRs)**, insurance **claims databases**, **patient registries**, **disease registries**, lab results, and even **mobile health/wearable device data**. These data contrast with the controlled data of RCTs: they may be less structured, observational, and subject to missingness and confounding. The FDA's framework defines RWD as data "routinely collected" from a variety of sources (pmc.ncbi.nlm.nih.gov).

When RWD are **analyzed** to generate clinical insights about a medical product – its use, benefits, or risks – the results are termed **Real-World Evidence (RWE)** (pmc.ncbi.nlm.nih.gov). RWE can inform many questions: population-level effectiveness, safety surveillance, comparative outcomes, and even serve as external controls or supplementary evidence in support of product approvals. For example, national death registries linked to clinical trials have been used to derive RWD endpoints (e.g. mortality) (www.fda.gov).

Historically, regulators have long used RWD under-the-hood (e.g. FDA's spinoff Sentinel Initiative began as a claims-monitoring system in 2008 (pmc.ncbi.nlm.nih.gov)). Over the last decade, however, interest in purposefully leveraging RWD/RWE for **regulatory submissions** has intensified. Legislative acts (like the US 21st Century Cures Act, 2016) explicitly directed agencies to evaluate RWE for new indication approvals and post-approval studies (pmc.ncbi.nlm.nih.gov). Key industry drivers include the high cost and time of RCTs (RCTs often consume >50% of a drug's development budget (www.fdli.org)), the need for evidence in patient subgroups or rare diseases where RCTs may be infeasible, and technological advances making large-scale data analysis possible. A 2017 Deloitte survey found over half of life sciences companies actively building RWE capabilities (www.fdli.org). RWE can accelerate product development by providing faster, more diverse evidence and by guiding trial design with historical benchmarks (so-called "target trial emulation" (pmc.ncbi.nlm.nih.gov)).

Figure 1 below contrasts key features of RWD/RWE versus RCT data. Importantly, neither is a universal replacement for the other; instead, they are increasingly seen as **complementary**. RCTs remain the gold standard for causal efficacy under controlled conditions, while RWE offers **external generalizability** and a broader evidence base, especially for safety and rare-event detection (pmc.ncbi.nlm.nih.gov).

Figure 1. *Characteristics of RCT vs. RWD/RWE.* While RCTs provide high internal validity via randomization and controlled protocols, their narrow inclusion criteria can limit generalizability. RWD offers large, heterogeneous real-world populations (including often underrepresented groups) (pmc.ncbi.nlm.nih.gov) (www.sciencedirect.com) but requires rigorous design and adjustments (e.g. propensity scoring) to mitigate biases. Regulatory-grade RWE must therefore ensure data quality and study rigour comparable to RCT standards (pmc.ncbi.nlm.nih.gov).

Definitions and Scope

For clarity, in this report we adopt standard definitions from the FDA and regulatory literature: **RWD** refers to routinely-collected health data (EHR, claims, labs, registries, etc.), and **RWE** refers to evidence obtained by analyzing RWD (pmc.ncbi.nlm.nih.gov). (Some reports use "Real-World Evidence" and "Real-World Data" interchangeably, but we distinguish them.) We focus primarily on **pharmaceutical** product development (drugs and biologics), though many principles apply to devices and diagnostics as well. "Regulatory-grade RWE" in our context implies evidence built under rigorous protocols, with attention to data provenance and analytic transparency, such that it meets FDA/EMA evidentiary expectations.

This report covers multiple aspects: historical perspective; current regulatory frameworks (FDA, EMA, etc.); technical infrastructure (data platforms, models, tools); methodological standards; and case studies of RWE in action. Each claim or fact is documented with peer-reviewed or regulatory sources. We include tables summarizing representative platforms and regulatory cases, and adopt an academic tone suitable for industry professionals, regulators, and policymakers.

Regulatory Landscape for RWE

U.S. FDA Initiatives

Legislative and Policy Foundations

The U.S. Food and Drug Administration has long used RWD in safety surveillance (post-market) and to inform certain decisions (www.fda.gov) (pmc.ncbi.nlm.nih.gov). However, a seminal moment was the **21st Century Cures Act of 2016**, which mandated that FDA establish an RWE program (pmc.ncbi.nlm.nih.gov). The law explicitly directed FDA to evaluate whether real-world evidence could support new indications for approved drugs or satisfy post-approval study requirements, noting that evidentiary standards should remain "substantial evidence" (pmc.ncbi.nlm.nih.gov). In response, the FDA in Dec 2018 released the first framework document for its RWE program (pmc.ncbi.nlm.nih.gov), outlining demonstration projects, guidance development, and stakeholder engagement.

The FDA further formalized its approach in guidance and regulations. Notably, in 2023 the FDA issued a final **Guidance for Industry on Real-World Data and RWE** (August 2023) (www.fda.gov), which updates prior draft guidance. This document emphasizes key considerations: pre-specification of study protocols, data quality and fitness-for-purpose, transparency of methods, and alignment with well-controlled study principles. Other FDA guidances have addressed related aspects, such as data standards for submissions containing RWD (www.pharmtech.com) and the suitability of specific data types (EHRs, claims) for regulatory use (in 2024) (www.pharmtech.com).

FDA Frameworks and Programs

The FDA's **RWE Program Guidance Document (2018)** laid out definitions and principles: RWD are "data relating to patient health status and/or the delivery of health care" from various sources, and RWE is clinical evidence derived from its analysis (pmc.ncbi.nlm.nih.gov). Thus, common sources include EHRs, claims, lab results, patient registries, and even digital device data (pmc.ncbi.nlm.nih.gov). The framework emphasized that existing regulatory standards (e.g. substantial evidence of effectiveness) still apply to RWE because such studies must be "adequate and well-controlled" if used to establish efficacy (pmc.ncbi.nlm.nih.gov).

FDA has also invested directly in data platforms. The **FDA Sentinel Initiative** (established 2008) is a distributed data network originally built for active safety surveillance. Sentinel's **RWE Data Enterprise (RWE-DE)** originally targeted EHR–claims linkage for at least 10 million individuals. An October 2024 report described the resulting Commercial Network covering 21 million lives and a separate Development Network covering 4.5 million lives (pubmed.ncbi.nlm.nih.gov). Similarly, the **FDA-Catalyst** program (pivoting from Sentinel) is exploring how to conduct pragmatic clinical studies in health systems.

In late 2024, FDA's Center for Drug Evaluation and Research (**CDER**) announced a **Real-World Evidence Innovation Center** (www.pharmtech.com). This new center (announced Dec 13, 2024) is charged with coordinating RWD initiatives, advanced analytics, and partnerships to scale regulatory use of RWE

(www.pharmtech.com). FDA also modernizes internally: adopting data standards (FDA's Data Standards Catalog now includes RWD elements) and guidelines like ICH E9(R1) ("estimands" in trials, applicable to RWE designs).

FDA officials have publicly addressed misconceptions and encouraged high-quality RWE. For example, an FDA senior leader clarified that FDA expects prespecified protocols, robust design, and understanding of biases whenever RWD is used in submissions. The FDA published on its website dozens of examples ("FDA use of RWE in regulatory decision-making" (www.fda.gov)) to illustrate how RWE has been applied (approvals, label changes, communications). Cases range from using single-arm trials with external controls to supplementing RCTs, to stand-alone RWD studies serving as confirmatory evidence (see Table 2 below).

Illustrative U.S. RWE Use Cases

In February 2021, FDA approved Nulibry (fosdenopterin) to reduce mortality risk in patients with molybdenum cofactor deficiency Type A. The study included RWD in both treatment and control arms; the treatment arm pooled participants from two single-arm trials and an expanded-access program (FDA evidence summary).

The original 2021 Voxzogo (vosoritide) indication was to increase linear growth in children aged five and older with achondroplasia and open epiphyses, under accelerated approval based on annualized growth velocity. The evidence package included a randomized placebo-controlled trial and two single-arm studies with external RWD controls (FDA evidence summary). FDA's ongoing accelerated-approval record retains a required study of final adult height.

In April 2023, FDA's Vimpat (lacosamide) review addressed a proposed loading-dose regimen. Efficacy was extrapolated for partial-onset seizures in patients aged one month to under 17 years and primary generalized tonic–clonic seizures in patients aged four to under 17 years; additional safety data were needed for the regimen. In all these examples, RWD sources (clinics, registries, claims) were subjected to rigorous analysis, and the FDA review team explicitly described the role of the RWE (e.g. as confirmatory or safety evidence) (www.fda.gov).

Table 2 (below) summarizes select case studies illustrating how RWD have been integrated into US regulatory submissions.

EMA and European Regulatory Initiatives

EMA's Big Data Strategy and DARWIN

The European Medicines Agency (EMA) and the broader European regulatory network have vigorously pursued RWE adoption. Early on, a **Joint HMA-EMA Big Data Task Force** (2017–2019) issued recommendations on using "big data" (RWD) for regulation. In 2020, the EMA published its own **Regulatory Science Strategy 2025** which emphasized fostering RWD use and data literacy. Crucially, EMA established **DARWIN EU** (Data Analysis and Real World Interrogation Network) – a public infrastructure linking distributed RWD sources across Europe. DARWIN (fully operational from 2023) coordinates queries to national healthcare databases, registries, and other sources to generate RWE for EMA committees (encepp.europa.eu). As of mid-2025, DARWIN EU had expanded from 20 to 30 data partners, reaching about

180 million patients across 16 European countries (encepp.europa.eu). This network makes available federated analyses on safety events, effectiveness, epidemiology, etc., at the request of regulators or public health bodies.

EMA also maintains a catalog of RWD sources and studies to enhance transparency. A July 2025 ENCePP news highlighted that 59 new multi-database RWD studies were conducted for regulatory use (Feb 2024–Feb 2025) – a 47% increase from the previous year (encepp.europa.eu). These studies addressed risk topics (e.g. vaccines, rare ADME interactions) and underscored regulators' proactive engagement in RWE generation. The EMA's **Big Data Steering Group** (replacing the earlier task force) regularly convenes stakeholders to advance data standards and methods across the EU (www.ema.europa.eu).

EMA Guidelines and Frameworks

EMA has published guidance on specific RWE methods. Its adopted Guideline on registry-based studies, first published on 26 October 2021, addresses studies using disease or condition registries to evaluate medicines' benefit-risk. Its reflection paper on RWD in non-interventional studies, first published on 3 April 2025, discusses methodological aspects of generating RWE for regulatory purposes. EMA's public information pages note that "scientific guidelines on real-world evidence aim to support use of RWD in regulatory decision-making" (www.ema.europa.eu). For instance, EMA (and its Committee for Medicinal Products for Human Use) has acknowledged that RWD can support **both pre-authorisation and post-authorization assessments** (e.g. for extensions or safety monitoring) (www.ema.europa.eu). However, the agency stresses that more experience and methods work are needed, and urges pharmaceutical sponsors to engage on study design.

Importantly, in 2020 the EMA-EunetHTA **OPTIMAL** framework (a European Health Technology Assessment report) investigated how RWE can underpin regulatory and HTA decisions. The EMA highlighted examples such as oncology treatments with external controls. Today, EMA tends to evaluate RWE on a case-by-case basis. For example, any RWE submitted in a Marketing Authorization Application (MAA) or line extension must adhere to standards akin to ICH guidance on study design (as the FDA does). However, with new European Medicines Regulatory Network strategy to 2028, EMA commits to further integrating RWE via DARWIN, methodological guidance, and collaboration with Health Technology Assessment bodies (encepp.europa.eu).

European Case Studies

Publicly available EMA examples of RWE use (beyond the DARWIN-generated studies) are fewer. However, some EU approvals have cited RWE. The EMA assessment for Cosentyx (secukinumab) describes randomized pediatric studies A2310 and A2311. The EMA's annual drug safety reports mention when patient chart reviews or registries complement trial data (e.g. in rare disease expansions). One analysis of EMA-authorised oncology drugs (2018–2022) noted that RWE was rarely the primary basis for efficacy decisions, but more frequently appeared in post-approval assessments or to address broader patient applicability (pmc.ncbi.nlm.nih.gov).

The role of RWE in EMA decisions continues to evolve. On July 1, 2025, EMA's dashboard celebrated a **47% year-over-year increase** in internal RWD studies, thanks in part to DARWIN's expanded reach (encepp.europa.eu). These examples show RWE informing public-health policy and regulatory monitoring across Member States.

Global and Multilateral Trends

Other regulators are also engaging RWE. Japan's PMDA and Health Canada have piloted RWE frameworks for supplementary approvals. Notably, an October 2023 article reported that FDA, EMA, PMDA (Japan), and China's NMPA found convergence on core principles like data quality and interoperability (www.linkedin.com). The IMI (Innovative Medicines Initiative) in Europe supports consortia (e.g. *EHDEN*) to harmonize RWD via the OMOP common model, anticipating linkage to DARWIN. The OECD and ICH (International Council for Harmonisation) have started dialogues on RWE guidelines.

In summary, regulatory bodies increasingly accept that fit-for-purpose RWE – derived from well-characterized platforms and networks – can play a role in approvals and safety. Both the FDA and EMA emphasize that rigorous study design remains paramount: RWE must align with good science (adequate controls, defined endpoints, minimized bias) (pmc.ncbi.nlm.nih.gov). What has changed is the ecosystem: billions of health records and analytical tools are now mobilized under regulatory-directed initiatives to produce the **"regulatory-grade"** evidence needed for decision-making.

Real-World Data Platforms and Networks

To generate regulatory-grade RWE, organizations rely on specialized platforms and networks that aggregate, standardize, and analyze RWD. These platforms span government-run surveillance systems, academic research networks, and commercial data providers. We categorize them as follows:

- **Government/Regulatory Networks**: Initiated or overseen by public agencies to support monitoring and research.
- **Academic Collaboratives**: Research consortia built around shared data models or federated queries.
- **Commercial Data Platforms**: Industry solutions providing access to curated RWD (and analytics software).
- **Integrated Health Systems**: Large hospital/EHR networks participating in RWE studies or direct partnerships.

Below we discuss selected examples of each category, focusing on their data scope and relevance for regulatory scenarios.

Government and Regulatory Data Networks

FDA Sentinel: The FDA's Sentinel System is a flagship RWE infrastructure. Initially launched to detect drug safety signals, Sentinel now encompasses automated queries of claims and EHR data from multiple partners (health plans, HMOs). By 2020, Sentinel covered data on over 100 million Americans. An October 2024 report on the **Sentinel RWE Data Enterprise** (RWE-DE) described the resulting EHR–claims-linked Commercial Network covering 21 million lives and a separate Development Network covering 4.5 million lives (project report). Sentinel has been directly used for FDA assessments: e.g. retrospective cohort analyses on drug safety in children (www.fda.gov). Its **distributed model** (data partners run local analyses per query protocols) preserves privacy while enabling regulatory studies. Sentinel's analytic toolkit (AQUA, common data model, statistical code libraries) is continuously developed by FDA's Sentinel Innovation Center.

DARWIN EU: As noted, DARWIN EU (Data Analysis and Real World Interrogation Network) is EMA's flagship network for evidence on performance and safety of medicines in Europe. It federates queries across national/regional databases, effectively acting as a *pharmacovigilance and outcomes research platform*. Participating sources include EHRs, hospital records, claims, disease registries across EU member states. Through a central coordination center, DARWIN can issue rapid studies (e.g., emergent vaccine safety) or planned analyses. By mid-2025, its expansion to 30 partners had reached ~180M European patients (encepp.europa.eu), making it a uniquely large RWD resource for regulators.

Other National Systems: Many countries maintain health-data networks. For example, the U.S. PCORnet (Patient-Centered Outcomes Research Network) is funded by PCORI and AHRQ: its 2025 population report describes health data from more than 50 million people nationwide through eight Clinical Research Networks and 78 partner organizations (PCORnet report). PCORnet uses a Common Data Model and supports comparative effectiveness and safety studies. European health services like the UK's CPRD (primary care database) or Nordic national registries are often tapped through collaborative studies. While not FDA/EMA-run, pharmaceutical sponsors frequently engage with these networks under regulated study protocols.

Academic and Consortium Platforms

OHDSI: The Observational Health Data Sciences and Informatics (OHDSI) initiative is an open-science global community that uses the OMOP Common Data Model to harmonize health databases (pmc.ncbi.nlm.nih.gov). OHDSI's federated approach enables investigators to run standardized queries on many databases (hospitals, claims, registries worldwide). Collectively, OHDSI sites cover hundreds of millions of patient records (estimates vary, but typically >500M globally). For example, OHDSI conducted multi-continental studies on COVID-19 therapies. OHDSI's relevance lies in its **open tools and validation efforts**, which align with regulatory needs for transparent, reproducible RWE (e.g., OHDSI released comparative effectiveness analyses replicating RCT results).

EHDEN: The European Health Data & Evidence Network (EHDEN) is a large IMI-funded project (now a foundation) to convert disparate European health data into the OMOP model. It aims to federate up to 35 countries' data for research. EHDEN underpins DARWIN by enabling data partners to participate (via common modeling). While EHDEN itself is not a 'platform' with an interface, it has built the network of harmonized data sites and created tooling for federated queries.

PCORnet: As noted, PCORnet is a U.S. network of Clinical Research Networks (hospitals, clinics) and Patient-Powered Research Networks, all using a shared CDM. It has broad longitudinal data on patients, and supports CER studies. For RWE platform purposes, PCORnet's strength is its diversity (multiple health systems, claims/EHR linkage) and its existing governance (HIPAA, IRB) already in place for research, making it attractive for corporate collaborations.

Commercial RWE Platforms

The private sector offers numerous RWE platforms combining data curation, analytic tools, and consulting. Key examples include:

- **TriNetX**: A global federated health research network backed by investment from Carlyle. It links de-identified EHR data from hundreds of health organizations in >20 countries (pmc.ncbi.nlm.nih.gov) . As of Dec 2025, TriNetX encompassed ~200 million patients across 170 institutions (pmc.ncbi.nlm.nih.gov) (clinics, hospitals). The platform provides real-time query tools (via a web interface) to design cohorts, do propensity matching, and generate response curves. TriNetX emphasizes its ability to replicate RCT findings in “real-world settings” and supports external control arm construction. (For example, a 2018 cardiovascular-outcomes study using TriNetX reported results consistent with randomized clinical trials.) The platform’s data updates continually, making it amenable to exploratory analysis and feasibility assessments.
- **Aetion Evidence Platform**: Aetion offers an analytics platform focused on automating observational research. It can link claims, EHR, registry and other data sources. FDA documents a research project using Aetion Evidence Platform to develop a framework and system of studies for rapid assessment of COVID-19 inpatient medical countermeasures (FDA project record). Aetion’s tools enforce study protocols and quality checks, aiming to meet “regulatory science” needs. The platform has been used by pharma companies for submission-grade studies. (Full details of patient counts are proprietary, but its business model often involves data contracts with insurers and networks.)
- **Flatiron Health**: Acquired by Roche, Flatiron maintains a large US oncology database tied to EHRs from cancer clinics. Flatiron’s network covers well over 3 million cancer patients (as of 2023) with detailed clinical notes. It provides analytics for oncology drug development and post-market studies.
- **IQVIA and SAS**: These life-science service firms offer integrated RWD solutions. IQVIA curates worldwide EHR and claims datasets (e.g., commercially-insured US claims, Medicaid/Medicare, Asian data, etc.) amounting to billions of records. It performs epidemiology analyses and can support submissions. SAS (Analytics software) has a data repository and tooling for pharmacoepi. These vendors often work behind the scenes on specific projects rather than open-platform style.
- **Others**: Medidata/Rave (Dassault) provides RWD connectors to its clinical trial platform, Syapse focuses on oncology and rare disease registries, etc. Newer entrants (e.g. Clarivate with TriNetX collaboration) continue to emerge.

Table A below summarizes key RWE data platforms and networks that are pertinent to regulatory RWE generation.

Table A. Selected RWE data platforms and networks.

Platform / Network	Type	Data Sources	Geographic Scope	Approx. Size / Notes
TriNetX	Commercial (Carlyle majority investment)	De-identified EHRs (clinical records)	Global (>20 countries)	~200 million patients (170 HCOs) (pmc.ncbi.nlm.nih.gov)
DARWIN EU	Regulatory (EMA)	National EHRs, claims, registries	Europe (16 countries)	~180 million patients (30 data partners; mid-2025 snapshot) (encepp.europa.eu)
FDA Sentinel	Regulatory	Claims data (Medicare, private)	U.S.	100+ million U.S. lives (distributed network)

Platform / Network	Type	Data Sources	Geographic Scope	Approx. Size / Notes
PCORnet	Academic/Consortia	EHRs + limited claims	U.S. (network)	More than 50 million patients (2025); 78 partner organizations; >13,000 sites of care (pcornet.org)
OHDSI/OMOP	Academic (open)	EHRs, claims, registries (mapped)	Global (numerous DBs)	Collective size many hundreds of millions (distributed)
Aetion Evidence Platform	Commercial	Claims/EHR/registries (via providers)	U.S., global datasets*	Used by FDA for COVID-19 RWE demo (news.aetion.com); scale depends on linked contracts
Flatiron Health	Commercial (Roche)	Onco EHR data, registries	U.S. (specialty clinics)	Millions of cancer patients
IQVIA	Commercial	Claims, EHR, Rx, lab data	Global	Billions of records (market claims/EHR)
EHDEN	Academic/Consortia	OMOP-mapped EHR/claims (federated)	Europe	Hundreds of data partners (OMOP conversion under way)
Local health networks	Mixed	Hospital/EHR system data	Varies (e.g. national)	e.g. NHS Digital (UK), Kaiser Permanente (US/Puerto Rico)

**Notes: Aetion partners with data providers (e.g. Ciox, claims vendors). FDA documents the platform's use in a COVID-19 medical-countermeasure research project (FDA project record). Flatiron's data reflect U.S. oncology practices, while IQVIA and others license regional datasets.*

This table is illustrative, not exhaustive. Each platform offers different capabilities: for example, **federated** networks (TriNetX, PCORnet) allow rapid cohort discovery and real-time estimates; OHDSI's distributed research community runs shared analyses locally and combines approved aggregate results while patient-level data remain under each partner's control; **rich disease registries** (Flatiron) provide depth of phenotyping. Platform selection depends on study needs (e.g. rare diseases vs broad outcome surveillance) and on data accessibility (licensing, location).

Data Standards and Technology

Underlying many platforms is the use of **common data models (CDMs)** and standardized terminologies. Examples include the OMOP CDM (used by OHDSI, TriNetX, EHDEN) and PCORnet CDM. These ensure data from diverse sources can be queried with the same codebook (diagnoses coded in ICD/MedDRA, procedures in CPT, LOINC for labs, etc.). FDA's Sentinel uses the Sentinel CDM, which is a precursor to OMOP. Initiatives also work on **FHIR** (Fast Healthcare Interoperability Resources) standards for health events, which agencies encourage for submitting EHR data. Data harmonization is vital: without it, cross-database studies (such as those run on DARWIN or OHDSI) would be infeasible.

To achieve “regulatory-grade” RWE, platforms additionally incorporate quality-checking and provenance tracking. For instance, data undergo cleaning (e.g. mapping free-text to codes) and validation (flagging improbable values). Platforms often exclude anonymized patient identifiers and apply governance controls. Analysis tools may include causal inference libraries (marginal structural models, g-methods) and enable **target-trial emulation** – explicitly framing an RWE study as if it were a hypothetical RCT, which many methodologists recommend (pmc.ncbi.nlm.nih.gov). Advanced platforms are starting to integrate AI: for example, natural language processing on clinical notes, or machine learning to predict missing values. Such AI is used to extract phenotypes and endpoints (e.g. identifying cancer stage from records). However, regulators have stressed the need for transparency and validation of AI methods in RWE contexts.

Overall, RWD platforms provide the infrastructure – from data ingestion to analysis pipelines – that allows industry sponsors to generate evidence in an **evidence-ready manner**. In the case of on-demand networks like TriNetX, investigators can conduct feasibility queries instantly (e.g. what percent of diabetic patients meet trial criteria?). More complex studies (e.g. a 12-month matched cohort analysis) typically require a project within a platform that follows pre-agreed protocols, often with third-party audit trails. Building and validating such platforms is an ongoing effort: for instance, FDA and partners continue to test synthetic control arms to ensure methods yield unbiased results.

Building Regulatory-Grade RWE

“Regulatory-grade” implies an evidence standard suitable for FDA/EMA evaluation. In practice, this means RWE must be generated under principles akin to those for RCTs, where applicable, and follow good research practices. Here we detail the components: data quality, study design, analysis, and governance.

Data Quality and Fitness-for-Purpose

The cornerstone of reliability is **data quality**. RWD sources vary widely in completeness and accuracy. For example, claims data reliably capture diagnoses related to billing, but lack detailed clinical labs; EHRs include rich clinical detail but may have heterogeneous coding and missingness. Registries may systematically collect certain outcomes but lack denominators. Each source has biases (e.g. claims include only insured patients). Regulatory agencies expect sponsors to rigorously assess **fitness-for-purpose**: the data must have relevant captured variables and sufficient follow-up to answer the question.

Best practices include data cleaning (e.g. standardizing units, resolving duplicates), curation to a CDM, and documentation of data provenance (when and how data were collected). Platforms may implement **data quality frameworks** (DQA) to check for completeness of key variables (e.g. age, gender, diagnosis codes), timeliness, and consistency. In sentinel-like networks, each data partner runs data checks and publishes results. For regulatory submissions, sponsors often include a data management plan describing these checks.

Metadata and lineage tracking are critical. EHR data often require extracting information from warehoused clinical systems. Linkages (e.g. connecting EHR and claims) must be validated (via patient IDs or probabilistic approaches) to ensure patients are not double-counted or mismatched. Missing data strategies must be pre-

specified – for example, if 30% of lab values are missing, how will that affect analyses? FDA guidance notes that RWD studies should transparently report data limitations and conduct sensitivity analyses (e.g. best/worst case scenarios) (pmc.ncbi.nlm.nih.gov).

Privacy is also a consideration. Regulatory-grade platforms typically use de-identified data or federated queries where patient-level identifiers never leave the data custodian. Assess privacy obligations for each dataset by jurisdiction, organisational role and identifiability. Under HIPAA, covered entities may disclose information meeting the de-identification requirements without Privacy Rule restrictions (HHS guidance). Under EU data protection law, truly anonymised data falls outside scope (EDPB explanation); pseudonymised data remains personal data subject to the GDPR (EDPB FAQ).

Study Design and Methodology

Designing an RWE study to support a regulatory claim requires **transparency and rigor**. Key elements include:

- **Pre-specified Protocols**: Though not FDA's own requirement, it is **strongly recommended** (and often required by FDA for RCTs) that an observational study be pre-registered and conducted under a written protocol (pmc.ncbi.nlm.nih.gov). The protocol should define objectives, endpoints, inclusion/exclusion criteria, data sources, statistical analysis plans, and sensitivity analyses. The FDA guidance and ICH E9(R1) emphasize this for clarity on "estimands".
- **Clear Objectives and Hypotheses**: What exact question is the study answering? Is it to demonstrate non-inferiority of a treatment to standard care, or to show event rate reduction compared to a historical baseline? The study design must align with the regulatory aim (e.g. new indication vs safety signal).
- **Comparative Study with Control**: Regulatory evidence typically demands comparisons. This may be internal (concurrent controls) or external. For RWE, external control arms (using RWD) are common when RCT controls are unavailable or unethical (pmc.ncbi.nlm.nih.gov). For example, in rare diseases or oncology, a historical control cohort from an RWD source can serve as a comparator. The **FDA/E10 guidance** cautions that external controls bring confounding and should only be used when large effects and predictable disease courses exist (pmc.ncbi.nlm.nih.gov). Thus, regulatory-grade RWE often involves sophisticated matching or stratification (propensity score matching, inverse probability weighting) to emulate randomization on observed confounders.
- **Addressing Confounding and Bias**: Unlike an RCT, observational RWD studies have no random allocation, so meticulous attention to confounding factors is essential (pmc.ncbi.nlm.nih.gov). Platforms and researchers use advanced methods – propensity scores, multivariable regression, high-dimensional confounder adjustment – to balance comparison groups on baseline risk factors. They may define a **target trial** and attempt to replicate its design in the observational setting (pmc.ncbi.nlm.nih.gov). Sensitivity analyses (e.g. negative control outcomes, quantitative bias analysis) can demonstrate robustness. Importantly, **data dredging must be avoided**: outcomes should not be chosen based on data inspection.

- **Endpoints and Follow-up**: The outcomes chosen must be carefully justified. Often only “hard” endpoints (mortality, hospitalization) are credible in RWD because they are reliably captured. Surrogate or subjective endpoints (pain scores, quality of life) are harder to measure from RWD sources. Regulatory-grade RWE should preferably focus on outcomes clearly recorded in the data. The time frame of follow-up must also match the study objective (e.g. 6-month mortality vs 30-day readmission).
- **Regulatory Benchmarks**: The **substantial evidence** threshold (21CFR314.126) still applies. An RWE study must be as rigorous as “adequate and well-controlled” trials in its essentials: clear group definition, bias control, and systematic outcome measurement (pmc.ncbi.nlm.nih.gov). Sponsors often discuss proposed RWE study designs with regulators ahead of submissions (through pre-IND or protocol assistance meetings) to align expectations.

Analytical Implementation

Once the design is set, execution involves statistical and computational steps:

- **Cohort Construction**: Using the platform’s query tools or code, investigators define inclusion/exclusion based on diagnoses, treatments, labs. For example, in TriNetX one might query “patients with myocardial infarction given Drug A, excluding those on Drug B.” The platform returns cohort counts and characteristics. Researchers will refine criteria to match the target population.
- **Worst-Case/Best-Case Analysis**: Analysts often run multiple statistical models. A primary analysis might use propensity-score-matched cohorts; a secondary analysis might use inverse-probability weighting or stratification. If a randomized subset exists, they may calibrate methods. All analyses should be pre-specified or, if changes are needed, fully documented with justification.
- **Transparency and Reproducibility**: Ideally, code and algorithms (e.g. for propensity scoring) are shared or made available. External reviews (or audits) of the analytics guard against p-hacking. In a submission, sponsors often include detailed statistical analysis plans.
- **Validation and Sensitivity Checks**: To build credibility, studies might include methods like emulating a known RCT or using a negative control outcome. For example, a drug-versus-internal-control analysis in RWD that replicates a published clinical trial result can bolster confidence. If an estimated effect is marginal, regulators may scrutinize whether residual confounding explains it. Therefore, sensitivity analyses (quantitative bias analysis) are important to show the effect is robust to unmeasured confounding assumptions.
- **Data Standards in Analysis**: Results and datasets for submission typically adhere to CDISC standards (the same standards used for clinical trials). For instance, a sponsor might convert the final analytical dataset to ADaM format or SDTM to integrate into the NDA/MAA submission. Use of standard terminologies (MedDRA for adverse events, LOINC for labs, etc.) is also expected to ensure consistency.

Governance and Ethics

RWE studies for regulatory use must also meet ethical standards. Even though data are de-identified, sponsors often obtain Institutional Review Board (IRB) or ethics committee rulings that the study poses minimal risk. Data use agreements must allow for research analysis. Patient privacy must be protected (for example, rare disease data may need statistical disclosure control).

Sponsors frequently involve patient or clinician experts in RWE planning. EMA has encouraged multi-stakeholder collaboration. In the U.S., networks like PCORnet include patient representatives; projects using Sentinel may involve community advisory groups. This stakeholder input can improve study relevance and ensure ethical oversight.

Data Analysis and Evidence

Trends and Statistics on RWE Use

Recent studies illustrate how RWE is entering regulatory practice:

- A 2025 study reviewed **218 approved FDA labeling expansions from January 2022 through May 2024** and identified available or potentially relevant RWE for **55 approvals**. FDA documents identified RWE for only **three approvals**; evidence for the other **52** was found through ClinicalTrials.gov and PubMed. The authors could not determine whether those externally identified studies were submitted or contributed to FDA decisions, so these results do not establish a submission-uptake rate or a trend in regulatory use (study).
- A 2020 literature review identified **27 case examples** (1998–2019) across FDA, EMA, PMDA, HC of regulatory approvals aided by RWD (www.sciencedirect.com). Of these, 17 were New Drug Applications (all orphan drugs) and 10 were line extensions (www.sciencedirect.com). Common data sources were medical records and registries. In nearly all cases the RWD either provided tolerability/efficacy evidence in lieu of a control arm or supplemented trial findings. Notably, drugs with RWE support tended to be orphan indications or oncology, reflecting situations where trials are challenging (www.sciencedirect.com).
- European simulation: One analysis focusing on rare disease MAAs (EMA) predicted that additional RWE could expand indicated populations compared to RCT-only submissions (joppp.biomedcentral.com). This supports the intuitive notion that RWE often includes sicker or broader patients than trial cohorts.
- On a broader scale, analytic market reports estimate that RWE solution platforms (software, data services) form a multi-billion-dollar market that is rapidly growing (projected to exceed $3–5B by 2030, though such figures come from market analysts rather than academic sources).
- From the regulator’s side, EMA reported 59 studies during February 2024–February 2025, up 47.5% from the previous reporting period (encepp.europa.eu). FDA’s own data portal (FAERS, Sentinel) now routinely incorporates external data queries.

These data points underscore key patterns: **RWE use is still niche but accelerating**, especially in orphan/oncology, and facilitated by new data capabilities. Regulatory agencies on both sides of the Atlantic are actively encouraging appropriate RWE, as evidenced by frameworks and studies.

Evidence from Case Studies

Beyond statistics, concrete examples illustrate how RWE can meet regulatory needs:

1. **Orphan/Registry-based Approvals**: FDA assessed Voxzogo using a randomized trial plus confirmatory evidence from externally controlled studies. Study 111-202/205 with its external control was not itself an adequate and well-controlled trial (FDA integrated review). The 2021 action used accelerated approval; FDA's ongoing record retains a final-adult-height study requirement.
2. **Post-Approval Efficacy Supplement**: Consider an example where a drug approved in adults seeks pediatric labeling. If pediatric RCTs are not feasible, sponsors have turned to RWE (sometimes from registries) to provide indirect evidence. (For instance, patient chart reviews might show how pediatric patients respond on standard care vs. expected growth.) Such extrapolation is governed by FDA/EMA pediatric guidance but RWE can reduce or replace clinical studies if properly validated.
3. **Safety Labeling Revisions**: RWE has long been used to update safety labels.
4. **Registered Trials Leveraging External Data**: In some trials (often single-arm registrational studies), RWD are woven into the primary analysis. For Nulibry, the treatment arm pooled participants from two single-arm trials with patients enrolled in an expanded-access program. The study included RWD in both treatment and control arms (FDA evidence summary).
5. **External Control Arm Feasibility**: Platforms like TriNetX advertise that they can construct an "external control arm" by matching real-world patients to a trial's inclusion criteria. A published Gerontology study, for example, used TriNetX data to replicate outcomes of a diabetes trial in a real-world cohort (propensity-matched) (pmc.ncbi.nlm.nih.gov). While this was a journal publication (not regulatory), it shows concept viability. Moreover, some regulatory submissions have cited TriNetX or similar networks to support control groups (even if details are often redacted in public documents).
6. **Multi-Region Studies for Vaccines/HTA**: The EMA has employed DARWIN for vaccine rollout evaluation (e.g. mpox vaccine analysis across EU) (encepp.europa.eu). Similarly, global networks enabled rapid RWE studies during the COVID-19 pandemic (e.g. on vaccine effectiveness or treatment comparators) that informed FDA/EMA decisions without conventional trials.

Each case underlines a principle: **fit-for-purpose RWE can either stand alone or complement trials**, but must be of high methodological quality. The FDA and EMA reviews explicitly categorize the "role of RWE" – whether confirmatory, supportive, or primarily safety-oriented (www.fda.gov). A reviewer's trust in RWE increases when its design mimics an RCT structure (with clear inclusion criteria, blinding of analysis where possible, and pre-specified endpoints) (pmc.ncbi.nlm.nih.gov).

Discussion of Implications and Future Directions

Regulatory Implications for Pharma

The increasing acceptance of RWE poses both opportunities and challenges for pharmaceutical companies:

- **Opportunity for Label Expansion**: RWE can unlock additional indications. For rare and hard-to-study conditions, demonstrating efficacy via RWE can achieve approvals that would otherwise stall. Companies can plan prospective generation of RWE (e.g. registry enrollment) alongside trials. Some sponsors have integrated post-market RWD collection as part of phase IV commitments, anticipating leveraging this data for post-approval indications.
- **Enhanced Pharmacovigilance**: Regulators are actively using RWE in safety surveillance (e.g. Sentinel for adverse events). This means pharma must ensure robust post-market RWD plans, including ready-to-analyze registries or EHR data collaborations. Speed of analysis is key: agencies now expect “near-real-time” monitoring (once a year increases in studies (encepp.europa.eu)). Some companies have partnered with networks like OHDSI or established private data hubs to conduct rapid safety queries.
- **Cost and Efficiency**: Well-designed RWE studies can reduce or replace some costly trials, lowering development costs and timelines. However, pharma must invest in capabilities: skilled epidemiologists, data scientists, and in-house or contracted platforms. Developing internal standards for RWE (analogous to GCP for trials) is underway in many firms. The return on investment depends on regulatory outcomes – if RWE enables even one additional or faster approval, it can be game-changing.
- **Data Access and Partnerships**: Access to RWD often requires partnerships. Pharma may need to collaborate with data vendors, healthcare systems, or institutions. For example, multi-sponsor initiatives have emerged (e.g. consortia for rare disease registries) to share RWD costs. Cross-industry standards and consortia (like Transcelerate’s RWE Corridor) aim to streamline access.
- **Regulatory Interactions**: The distinct evidentiary context of RWE means that regulatory scrutiny will differ. Submissions involving RWE should provide detailed methodology. The FDA’s RWE guidance suggests early interaction (pre-IND or meeting requests) to align on analysis plans. In the EU, it is prudent to engage with EMA’s patient registries or scientific advice committees when using RWD for label changes.

Challenges

- **Heterogeneity of Data**: Even with CDMs, underlying differences (different healthcare systems, variable coding practices) create residual heterogeneity. Ensuring that an external control arm built from one country’s registry truly matches a trial population from another country is nontrivial. Cross-jurisdictional RWE (e.g. global studies) require careful calibration.

- **Bias and Uncertainty**: Nonrandomized observational RWE lacks randomized treatment assignment. RWE can also come from randomized trials that collect outcomes through RWD sources (FDA explanation). Unmeasured confounding can never be entirely ruled out. Skeptical reviewers will question any RWE analysis that yields moderate effect sizes. The threshold for "dramatic effects only"—as per E10 guidance (pmc.ncbi.nlm.nih.gov)—is sometimes interpreted strictly by regulators (some believe only large effects will be accepted without RCT). Achieving regulatory acceptance with modest effect sizes will remain difficult without some random component or novel quasi-experimental design.
- **Regulatory Acceptance Variability**: FDA and EMA still have different cultures. Historically, FDA has been more open (21st Cures Act) to RWE for drug efficacy, while EMA has been more conservative (except for safety). Sponsors must tailor RWE strategies accordingly. For example, an approval supported mainly by RWE might be more plausible in the U.S. for a supplemental indication than in the EU.
- **Ethical and Legal**: GDPR and data protection laws in Europe impose strict requirements on patient data use. Even de-identified data can be sensitive if rare conditions are involved. Ensuring compliance can slow projects. On the ethics front, there's debate on when RWD studies require patient consent.
- **Quality Standards and Harmonization**: There is no single "RWE regulatory standard". Agencies and industry are still converging on best practices. For instance, should RWE protocols be registered (like clinicaltrials.gov)? Should analyses be audited by external parties? Ad hoc, one-off RWE studies may be harder to validate than large, pre-specified trial-like studies. The professional community (e.g. ISPE, ISPOR) is working on checklists and "good RWE practice" standards (see sidebar below).

> **Sidebar: RWE Methodology Standards (examples)**
>
> - **ISPE Good Pharmacoepidemiology Practices (GPP)** – principles for design and reporting of observational drug-outcome studies.
> - **FDA Guidance on Sentinels/Registries** – e.g. using registries for stemi for device approvals.
> - **ICHE9(R1) / Estimands** – framework to define treatment effects in complex settings (applies to RWE trial emulations too).
> - **Target Trial Emulation Framework** – explicit design-based framework to mimic an RCT using observational data (pmc.ncbi.nlm.nih.gov). Sponsors and regulators may require evidence that these and related guidelines were followed.

Future Trends

Looking ahead, several developments will shape regulatory-grade RWE:

- **AI and Advanced Analytics**: Machine learning will play a growing role in RWE generation. For example, NLP algorithms can extract endpoints (e.g. identifying disease progression from radiology reports) that are not coded. Predictive models can flag safety issues earlier. However, regulators will demand validation: black-box models must not obscure study reproducibility. FDA's recent interest in AI (through the CDER Real-World Evidence Innovation Center) suggests more guidance is forthcoming on trustworthy AI in clinical evidence generation (www.pharmtech.com).

- **Wearables and Digital Biomarkers**: New RWD sources (smartphone data, wearables) are just starting to be used for endpoints like activity or sleep quality. In time, these could supplement RWE platforms, especially in chronic diseases. For example, continuous glucose monitors generate real-world glycemic data. Regulators will need to establish how to incorporate and validate these novel data streams.
- **Global Data Integration**: Currently, each platform is often region-specific. Future trends include better cross-platform interoperability. The fact that FDA, EMA, PMDA, and NMPA align on many RWE principles (www.linkedin.com) may lead to more international RWE studies, where a single federated analysis pool data from multiple countries' EHRs. Initiatives like ICMRA (International Coalition of Medicines Regulatory Authorities) have begun discussing global RWE networks.
- **Regulatory Guidance Harmonization**: Harmonized guidance already exists for non-interventional RWD studies assessing medicines' safety. ICH M14 reached Step 4 adoption on 4 September 2025, and CHMP adopted the final Step 5 guideline on 18 September 2025 (final guideline). Future harmonization for other RWE applications should be distinguished from this existing safety-study guidance.
- **Commercialization of RWE Platforms**: The RWE analytics industry is expanding, with new entrants and consolidation (e.g. Datavant acquiring Aetion). Cloud computing and data-sharing technologies (e.g. secure multi-party computation) will lower barriers. Pharma may increasingly subscribe to integrated RWE services rather than build them in-house.
- **Education and Culture**: Both clinicians and regulators are learning about interpreting RWE. Over time, familiarity will increase trust, especially if high-profile successes accumulate. Training programs (e.g. joint academia-industry RWE workshops) are proliferating.

Tables

Table 1: Key RWE Data Platforms and Networks

Platform/Network	Type/Operator	Data Sources	Coverage	Regulatory Relevance
TriNetX	Commercial (Carlyle, majority investor as of January 2025)	De-identified EHRs from hospitals/clinics	Global (20+ countries)	Used for protocol feasibility, external controls; trials at U.S. FDA (pmc.ncbi.nlm.nih.gov)
DARWIN EU	Public (EMA/EU HMA-EMA)	National EHRs, claims, registries	Europe (16 countries)	Provides RWE to EMA committees; 180M patients (2025) (encepp.europa.eu)
FDA Sentinel	Public (FDA)	Claims databases (Medicare, commercial)	USA (distributed network)	Used in post-market safety; expanded to EHR (RWE-DE project) (pubmed.ncbi.nlm.nih.gov) (www.fda.gov)
PCORnet	Academic network (USA)	EHR & some claims from multiple centers	USA (>50 million patients; 2025 snapshot)	Supports comparative effectiveness research; used in pediatrics and chronic disease studies (pcornet.org)

Platform/Network	Type/Operator	Data Sources	Coverage	Regulatory Relevance
OHDSI/OMOP	Academic/open consortium	EHR, claims, registries (mapped to OMOP)	Global (hundreds of DBs)	Enables multi-database RWE studies; methods validated against trials (pmc.ncbi.nlm.nih.gov)
Aetion Evidence Platform	Commercial (Aetion/Datavant)	EHR, claims, registries via third parties	US/global (via vendors)	FDA contracted Aetion for COVID-19 RWE; platform used for submission-grade analyses (news.aetion.com)
Flatiron Health	Commercial (Roche)	Oncology clinic EHR, labs, pathology	USA (oncology focus)	Used in oncology drug submissions and outcomes research (e.g., comprehensive cancer registries)
IQVIA Real-World Solutions	Commercial	Insurance claims, EHR, prescriptions, labs	Global	Provides real-world evidence studies (HMA-EMA catalogue entry)
National/Local Systems	Mixed (gov't & academic)	EHR/claims (e.g. NHS Digital, Kaiser)	Varies (nationwide)	Often used in RWE studies (e.g. UK CPRD for NICE/EMA; Kaiser data for FDA dialogue)

Table 2: RWE Use Cases in Regulatory Submissions

Drug/Study	Regulatory Context	RWD Source(s)	Study Design / Role of RWE	Reference
Voxzogo (vosoritide) – increase linear growth in children aged five and older with achondroplasia and open epiphyses (original 2021 indication)	FDA accelerated approval (2021), based on annualized growth velocity; final-adult-height study required	Achondroplasia Natural History registry	Randomized placebo-controlled trial plus externally controlled single-arm studies supplying confirmatory evidence	2021 FDA label; FDA integrated review; ongoing requirement
Nulibry (Fosdenopterin) – MoCD Type A	FDA NDA (2021)	Medical records, including expanded-access program data	Externally controlled trial; treatment arm pooled participants from two single-arm trials and an expanded-access program; RWD included in both treatment and control arms	FDA evidence summary
Vimpat (Lacosamide) – pediatric epilepsy *(loading dose)*	FDA sNDA (2023)	PEDSnet network (EHR data)	Retrospective cohort (safety analysis for new regimen in children); supportive data for dosing (www.fda.gov)	FDA prescribing information: alternate initial dosing regimen

Drug/Study	Regulatory Context	RWD Source(s)	Study Design / Role of RWE	Reference
Orencia (abatacept) – prevention of acute graft-versus-host disease, with a calcineurin inhibitor and methotrexate, in patients aged two and older receiving a matched or one-allele-mismatched unrelated-donor hematopoietic stem-cell transplant	FDA supplemental BLA (2021)	CIBMTR registry	Randomized trial for matched unrelated donors plus a non-interventional study for one-allele-mismatched unrelated donors	FDA label; FDA evidence summary
Actemra (tocilizumab) – hospitalized adults with COVID-19 receiving systemic corticosteroids and requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO	FDA supplemental BLA approval (December 21, 2022)	National death records	Randomized controlled trial using RWD to evaluate the primary endpoint of 28-day mortality	FDA approval record; FDA label; FDA evidence summary

(FDA references correspond to publicly available summaries, as cited in the FDA RWE tables (www.fda.gov).)

Conclusion

The landscape of drug development and regulation is undergoing a **significant transformation** as real-world data and evidence become integral to decision-making. Through extensive legislative, regulatory, and scientific initiatives, both FDA and EMA are constructing an ecosystem where **“regulatory-grade” RWE** – credibly generated from large-scale platforms – complements clinical trials. This report has detailed the historical drivers (e.g. 21st Century Cures, EMA Big Data) and current structures (DARWIN EU, Sentinel, TriNetX, etc.) supporting this shift. We have shown that, when properly designed and executed, RWE studies can meet evidentiary thresholds: they have already contributed to approvals, label expansions, and safety actions cited by regulators (www.fda.gov).

Pharmaceutical companies must adapt by investing in data platforms, analytics expertise, and rigorous research methods. The **ultimate goal** is improving patient outcomes: by leveraging RWE, sponsors can address clinical questions unanswerable by trials alone – such as long-term safety in diverse patient pools, or treatment effectiveness in the real world. As FDA and EMA continue to issue guidance on data quality and study design (e.g. 2023 FDA guidance, ongoing EMA reflections), the bar for “regulatory-grade” RWE will become clearer. Stakeholders must stay engaged: from contributing high-quality data to these platforms, to developing best-practice standards.

In coming years, we anticipate greater **harmonization** between U.S. and EU requirements for RWE, as regulators globally recognize common principles of data reliability and transparency (www.linkedin.com). Technological advances – AI for data curation, federated analytics across borders, digital biomarker integration – will further enhance capabilities. Ultimately, this convergence of data, technology, and regulation holds promise for more efficient drug development and regulatory review. Companies and regulators alike must maintain a balanced approach: embracing innovation in RWE, while upholding the scientific rigor essential to patient care.

References: (All claims above are supported by cited literature and regulatory documents, as indicated by the in-text citations.)

Source links

Links cited in this article, in order of first appearance. Full addresses are provided for readers using extracted text.

1. https://pmc.ncbi.nlm.nih.gov/articles/PMC7687199
2. https://www.pharmtech.com/view/industry-outlook-for-2025-real-world-data
3. https://pmc.ncbi.nlm.nih.gov/articles/PMC12446098
4. https://encepp.europa.eu/newsroom/news/use-real-world-evidence-regulatory-decisions-new-report-shows-47-rise-ema-real-world-data-studies-2025-07-01_en
5. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-improve-growth-children-most-common-form-dwarfism
6. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214018s000lbl.pdf
7. https://pmc.ncbi.nlm.nih.gov/articles/PMC8697198
8. https://www.fda.gov/science-research/real-world-evidence/fda-use-real-world-evidence-regulatory-decision-making
9. https://www.fdli.org/2018/08/update-fdas-historical-use-of-real-world-evidence
10. https://pmc.ncbi.nlm.nih.gov/articles/PMC11931024
11. https://www.sciencedirect.com/science/article/pii/S0149291820301338
12. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug
13. https://pubmed.ncbi.nlm.nih.gov/39385712
14. https://www.fda.gov/science-research/real-world-evidence/cder-drug-approvals-used-real-world-evidence
15. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214938s000lbl.pdf
16. https://www.fda.gov/drugs/accelerated-approval-program/ongoing-non-malignant-hematological-neurological-and-other-disorder-indications-accelerated
17. https://www.ema.europa.eu/en/events/joint-hma-ema-big-data-steering-group-workshop-rwe-methods
18. https://www.ema.europa.eu/en/scientific-guidelines/guideline-registry-based-studies-0
19. https://www.ema.europa.eu/en/scientific-guidelines/reflection-paper-use-real-world-data-non-interventional-studies-generate-real-world-evidence
20. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-guidelines/clinical-efficacy-safety-guidelines/real-world-evidence
21. https://www.ema.europa.eu/en/documents/variation-report/cosentyx-h-c-3729-ii-0057-epar-assessment-report-variation_en.pdf
22. https://pmc.ncbi.nlm.nih.gov/articles/PMC12836655
23. https://www.linkedin.com/posts/alexandros-sagkriotis_rwe-rwd-regulatoryscience-activity-7386682292607545345-YwCP
24. https://pcornet.org/data/2025population-insights
25. https://www.carlyle.com/media-room/news-release-archive/carlyle-makes-strategic-growth-investment-trinetx-acquires-majority
26. https://pmc.ncbi.nlm.nih.gov/articles/PMC12821341

27. https://pmc.ncbi.nlm.nih.gov/articles/PMC6304296
28. https://www.fda.gov/emergency-preparedness-and-response/preparedness-research/using-real-world-evidence-advance-covid-19-medical-countermeasures
29. https://www.prnewswire.com/news-releases/trinetx-appoints-new-members-to-board-of-directors-301232090.html
30. https://pcornet.org/resources/data-reports
31. https://news.aetion.com/fda-aetion-rwe-advance-regulatory-science-innovation
32. https://www.ohdsi.org/data-standards
33. https://www.hhs.gov/hipaa/for-professionals/special-topics/de-identification/index.html
34. https://www.edpb.europa.eu/topics/ai-and-technology/anonymisation-pseudonymisation_en
35. https://www.edpb.europa.eu/contact/frequently-asked-questions_en
36. https://joppp.biomedcentral.com/articles/10.1186/s40545-022-00433-z
37. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214938Orig1s000IntegratedR.pdf
38. https://www.fda.gov/news-events/fda-voices/realizing-promise-real-world-evidence
39. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m14-guideline-general-principles-planning-designing-analysing-reporting-non-interventional-studies-utilise-real-world-data-safety-assessment-medicines-step-5_en.pdf
40. https://trinetx.com/press-releases/trinetx-founding-ceo-announces-plans-to-step-down
41. https://catalogues.ema.europa.eu/institution/49756
42. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/022253s050%2C022254s040%2C022255s032lbl.pdf
43. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125118s240lbl.pdf
44. https://www.fda.gov/media/150319/download
45. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125276s138lbl.pdf

THE PUBLISHER

About IntuitionLabs

IntuitionLabs is an AI consulting, custom software development and data engineering firm serving pharmaceutical, biotechnology, medical-device and other life-science organizations. We work with clinical, regulatory, medical-affairs, commercial, quality and IT teams to connect technology decisions with the work people need to accomplish.

AI consulting and adoption

Our AI enablement services cover readiness assessments, use-case selection, governance and policies, team workshops, adoption measurement and ongoing advisory support. We help organizations structure the information layer behind AI: source material, context, permissions and maintained knowledge that make generated answers useful and reviewable. Private LLM inference and hosted AI options support teams evaluating how to operate AI with appropriate control over their data and infrastructure.

Software, data and life-science workflows

IntuitionLabs develops custom software for pharma and biotech, integrates enterprise systems, and builds data engineering and business intelligence solutions. Areas of focus include AI agents, regulatory research, medical writing, medical affairs, CMC information, competitive intelligence and clinical-document workflows. Our eTMF intelligence work includes cross-system reconciliation and inspection-readiness support.

Enterprise platforms and regulated delivery

We provide Veeva services, application support, managed services, integrations and custom applications, alongside enterprise content work involving platforms such as Egnyte. For regulated workflows, our services include GxP enablement, computer-system validation and software development addressing 21 CFR Part 11 requirements. The applicable controls, validation responsibilities and acceptance criteria are defined for each engagement.

Work with IntuitionLabs

Explore AI enablement, pharma and biotech software development, data engineering and BI, and Veeva services. Contact IntuitionLabs to discuss your workflow, information sources and implementation needs.

IntuitionLabs publishes educational research to help life-science teams make informed technology decisions. Coverage of a product or organization does not imply a client relationship, endorsement or partnership.

Website: https://intuitionlabs.ai

This article is educational. Verify consequential medical, legal, financial, regulatory and technical decisions with appropriate professionals and the cited primary sources. Company services are described separately from the article's research findings.