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Review Article

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Regulatory Development, Adoption, and Perseverance of Real-world Evidence with global health authorities

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Abstract

Real-world evidence (RWE) has gained significant attention as a valuable source of evidence in healthcare decision-making. This article provides a comprehensive analysis of the regulatory development, adoption, and perseverance of RWE with global health authorities, as well as a synopsis of the major trends and practices among global health authorities. The aim is to shed light on the current landscape, and prospects of utilizing RWE in regulatory processes. Globally, many health authorities are drafting guidelines for RWE and implementing various regulations. Implementation is in the initial stages because RWE has certain limitations. This article examines the experiences of selected global health authorities in the development and implementation of RWE strategies. It also examines regulatory guidelines, pilot programmes, and collaborations designed to establish a solid foundation for the use of RWE. However, despite all challenges and limitations, RWE is widely being used in drug approval and commercial sense.

Keywords: Real-world evidence (RWE), Clinical Trials, randomized controlled trials (RCTs), FDA, CBER, PMDA, TMDA, ICH, Covid-19, Health Canada

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1. Introduction

McKinsey estimates that by adopting advanced real-world evidence (RWE) analytics across its value chain, an average top twenty pharmaceutical company could unlock more than $300 million per year over the next three to five years. As a result, multiple stakeholders, including regulators, payers, and life science organizations, have increased their focus on the development and use of RWE to improve the commercial and scientific value of drugs for patients and prescribers alike. (1,2) While clinical trials continue to be a vital component of the drug approval process, confirming the safety and efficacy of drug products, health authorities around the world are adopting novel RWE-based mechanisms for drug approval. (3)

This article provides an overview of the evolving landscape of regulatory development, adoption, and perseverance of RWE with global health authorities. In recent years, there has been a paradigm shift in healthcare decision-making, with an increasing recognition of the value of RWE. Regulatory frameworks and initiatives have been evolving to accommodate the integration of RWE into the regulatory decision-making process.

However, the utilization of RWE in regulatory processes is not without its challenges. Data quality, privacy concerns, standardization, and methodological rigor are among the key issues that need to be addressed. Health authorities have been actively working on solutions to overcome these challenges and ensure the reliability and validity of RWE. The demand for robust and reliable evidence beyond traditional randomized controlled trials (RCTs) has been growing in the healthcare field. (4) Real-world evidence (RWE) has emerged as a promising source

of information to address gaps in knowledge regarding the safety, efficacy, and effectiveness of medical interventions. Regulatory agencies play a crucial role in shaping the adoption and application of RWE in decision-making processes. (5,6)

2. Difference between Real world Evidence and standard clinical trials

Unlike clinical trials, RWE requires aggregating various sources of data available through routine clinical practice. Clinical trials involve recruiting a group of participants meeting specific criteria and are meticulously designed for scientific rigor. They ensure that new drugs are safe and effective before going to market. In contrast, RWE is based on real-world data, variable patterns, and heterogenous groups using multiple interventions. (7) RWE trials do not require patient recruitment, ethical committee approvals, safe research on larger groups, or comparatively longer durations. The number of RWE-based trials is increasing every year. The table below provides a comparison of RWE to Clinical Trial (8):

Table 1: Comparison between RWE and Standard Clinical Trials

Comparison Point	Real-world Evidence (RWE)	Standard Clinical Trials
Type of data collected	Data collected from various sources outside of traditional randomized controlled clinical trials (RCTs).	Studies conducted in a controlled environment with strict inclusion and exclusion criteria.
Patient population inclusivity	Includes data from a broader population, including patients with comorbidities and other factors excluded from clinical trials.	Typically enrolls a select group of patients who meet strict criteria.
Study environment	Provides insights into how a drug performs in a real-world setting.	Collects data over a relatively short period.
Data collection scope	Includes data from a patient's entire course of treatment, including long-term outcomes and adverse events.	May not capture long-term outcomes or rare adverse events.
Representation of subpopulations	Provides insights into subpopulations that may not be well-represented in RCTs.	May not provide enough data on specific subpopulations.
Study purpose	Can provide insights into the effectiveness of treatments in routine clinical practice.	Provides a controlled environment to demonstrate a drug's safety and efficacy under ideal conditions.
Study design	Observational and subject to various biases and confounding factors that can impact the validity of the results.	Designed to minimize biases and confounding factors.
Limitations and challenges	Can lack the control and standardization of clinical trials, making it challenging to draw definitive conclusions.	Can be time-consuming and expensive.

3. Global Status in different countries

3.1 US

A comprehensive investigation was conducted in order to improve our understanding of the historical use of Real-World Evidence (RWE) in FDA submissions. The objective was to identify instances in which RWE had been implemented and assess its impact. The following assessments are carried out during the review:

- The Drugs@FDA database and the Center for Biologics Evaluation and Research Biological Approval (CBER BLA) list were extensively examined to pinpoint examples of RWE implementation. Specific criteria were applied to select drugs for analysis, including factors such as efficacy, supplements, new molecular entities, new active ingredient submissions, and unlabeled submissions. (9, 10)
- Rigorous scrutiny was applied to approval letters, prescribing information, and medical or multi-disciplinary reviews. Keywords indicative of the utilization of RWE were sought to determine the presence of any of the four FDA-approved methods.
- The review period spanned from January to July 2020. A total of 273 drugs from Drugs@FDA and 9 drugs from CBER BLA approvals met the criteria for inclusion in the keyword search.
- Out of the 282 regulatory submissions examined, it was determined that 77 unique products, representing approximately 27.2% of the drugs analyzed, integrated RWE into their regulatory submissions.
- The analysis revealed that the incorporation of RWE in regulatory submissions could be categorised into four groups: 17 instances of single-arm trials employing RWE as an external control, six instances involving biosimilars, 13 cases involving accelerated approvals, and nine breakthrough therapies (11)

This exhaustive investigation shed (Figure 1) light on the prevalence and diverse applications of RWE in FDA submissions, highlighting its value as a regulatory tool.

3.2 EMA

The European Medicines Agency (EMA) published the EMA Regulatory Science to 2025 report in 2020, which emphasized the significance of using high-quality real-world data (RWD) in regulatory decision-making. The report highlighted RWD promotion in regulatory processes as one of its top recommendations. The EMA created the OPTIMAL framework to address the operational, technical, and methodological challenges

associated with RWD. This framework provides a set of criteria for the application of RWD regulations.

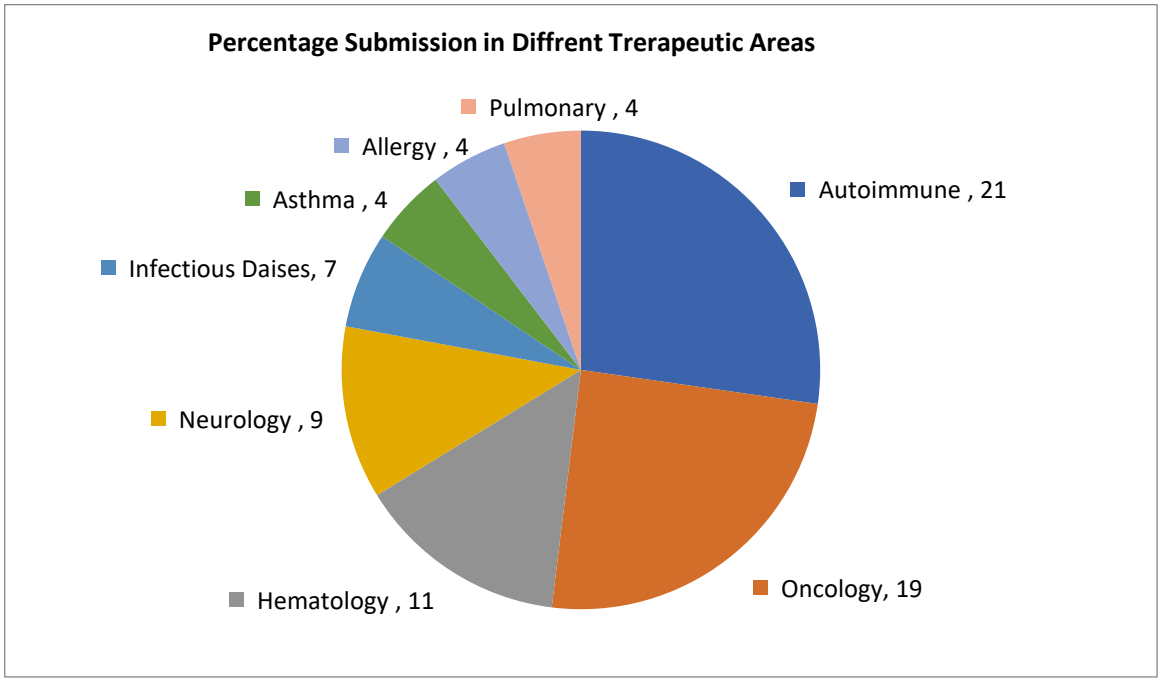

Figure 1. Percentage Submission in different Therapeutic areas

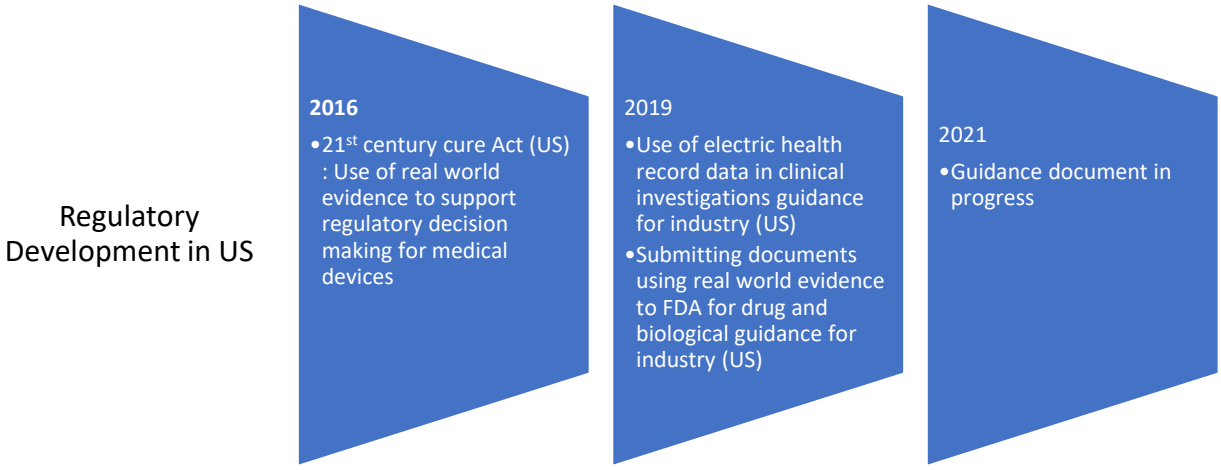

Figure 2. Current progress about the US Regulatory Affairs Development

While there is a growing recognition of the need to include RWD in regulatory submissions, efforts have been made to establish its appropriate usage boundaries, the development of concrete guidelines continues to be a strategic priority. As a result, the incorporation of RWD in regulatory submissions is still uncommon, with its use primarily limited to post-approval research and safety monitoring. (12)

Recent evidence proposing the medicine adoption model has demonstrated the potential benefits of integrating RWD alongside clinical trials at the regulatory stage. This model suggests that the early generation of RWD in conjunction with clinical trials could increase maximal adoption by 31 patients per 100 trial patients and reduce the time to maximal adoption by 22 months per 100 trial months. Such findings highlight the substantial benefits pharmaceutical companies and patients can derive from utilising RWD in the earliest phases of drug development. (13-15) Table 2 enlist few examples of drug approved by EMA with RWE.

Table 2. Examples of drug approved by EMA with RWE

Trade name	Year of approval
Alipogene tiparvovec (Glybera)	2012
Cholic Acid (Orphacol)	2013
Zalmoxis	2016
Strimvelis	2016

Tisagenlecleucel (Kymriah)	2018
Axicabtageneciloleucel (Yescarta)	2018
Alglucosidase alfa (Myozyme/Lumizyme)	2006
Certiponase alfa (Brineura)	2017
Blinatumomab (Blincyto)	2015
Avelumab (Bavencio)	2017

3.3 Japan

Japan has well-established ethical guidelines for clinical research, including "Ethical Guidelines for Medical Research Involving Human Subjects" and "Ethical Guidelines for Human Genome/Analysis Research". Subsequently, these guidelines were merged, and in 2021, new "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" guidelines were published. The Japanese pharmaceutical industry, particularly the Japan Pharmaceutical Manufacturers Association (JPMA), frequently cites these new integrated guidelines in their submissions for Real-World Evidence (RWE) studies.

In Japan, the Agency for Medical Research and Development (AMED), along with regulatory authorities and pharmaceutical companies, actively promotes the implementation of RWD through discussions and advocacy. The establishment of a Clinical Innovation Network (CIN) has been instrumental to these efforts. The "Basic Approach to the Use of Medical Information Databases in Post-Marketing Pharmacovigilance" was published in June 2017 to outline the framework for using medical information databases in post-marketing surveillance. The Pharmaceuticals and Medical Devices Agency (PMDA), as the regulatory body, strongly advocates for the use of RWD and RWE in regulatory affairs, particularly through the use of post-marketing research databases.

These developments demonstrate Japan's commitment to advance the use of RWD and RWE in regulatory decision-making processes and post-marketing surveillance activities. The collaboration between AMED, regulatory authorities, and the pharmaceutical industry represents a concerted effort to capitalize on RWD's potential in ensuring the safety and efficacy of medical products in Japan. (16) The examples of Japanese MLDAs that have been approved based on RWE are provided in Table 3.

Table 3. Japanese MLDAs approved based on RWE

Product	Indication	Approval Year
Asfotase alfa	Hypophosphatasia	2015
Avelumab	Markel cell carcinoma	2017
Cerliponase alfa	Neuronal ceroid-lipofuscinois	2017
Paliperidone Palmitate	Schizophrenia	2018
Palbociclib	Male breast cancer	2019
Selinexor	Multiple myeloma	2019
Erdafitinib	Urothral carcinoma	2019

3.4 Canada

Health Canada has implemented several drug regulation initiatives to establish the use of real-world evidence (RWE) and real-world data (RWD). Health Canada conducted a joint workshop with the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2018, launching an initiative to integrate RWE throughout the drug life cycle. This workshop also examined the advantages of implementing RWE as well as the challenges associated with its implementation.

Health Canada published a report titled "Optimizing the Use of Real-World Evidence to Inform Regulatory Decision-Making" on April 16, 2019, recognizing the increasing global use of RWE to assess the safety, efficacy, and effectiveness of drugs for regulatory decisions. A companion document titled "Elements of Real-World Data/Evidence Quality Throughout the Prescription Drug Product Life Cycle" outlined the standards identified by Health Canada as essential for informing regulatory decisions. It also acknowledged that certain diseases or disorders, such as rare diseases, present challenges for conducting randomized controlled trials (RCTs), making RWE-based studies suitable as supporting evidence.

In March 2020, Health Canada, in collaboration with CADTH, published a strategy document that outlined the operationalization of incorporating RWD/E into decision-making processes. Furthermore, on December 3, 2019, Health Canada and the Canadian Society of Pharmaceutical Sciences (CSPS) organized a workshop on the "Use of Real World Data/Evidence to Inform Regulatory Decision Making." Experts from FDA, EMA, Health Canada, industry, and academia participated in discussions on the advantages and disadvantages of using RWE. The consensus among the experts was not whether RWE would be integrated into regulatory decision-making, but rather focused on the appropriate timing and methods to leverage RWE while maintaining a high standard of evidence. (17) These initiatives and workshops demonstrate Health Canada's commitment to advancing the use of RWE in regulatory decision-making processes. (18,19)

3.5 Taiwan

"Food and Drug Administration, Ministry of Health and Welfare, Executive Yuan" (TFDA) is responsible for reviewing and approving drug clinical trial applications in Taiwan. On 1 June 2011, the TFDA established the "Integrated Medicinal Product Review Office" (iMPRO)

in order to integrate the CDE and TFDA review processes. TFDA (or CDE delegated by TFDA) is the contact window for clinical trial applications. These clinical trial applications include protocol reviews, protocol amendments, bridging study evaluations (BSE), and official letters pertaining to regulation issues. (20) Figure 3 illustrates TFDA's guidelines and announcements. from the TFDA

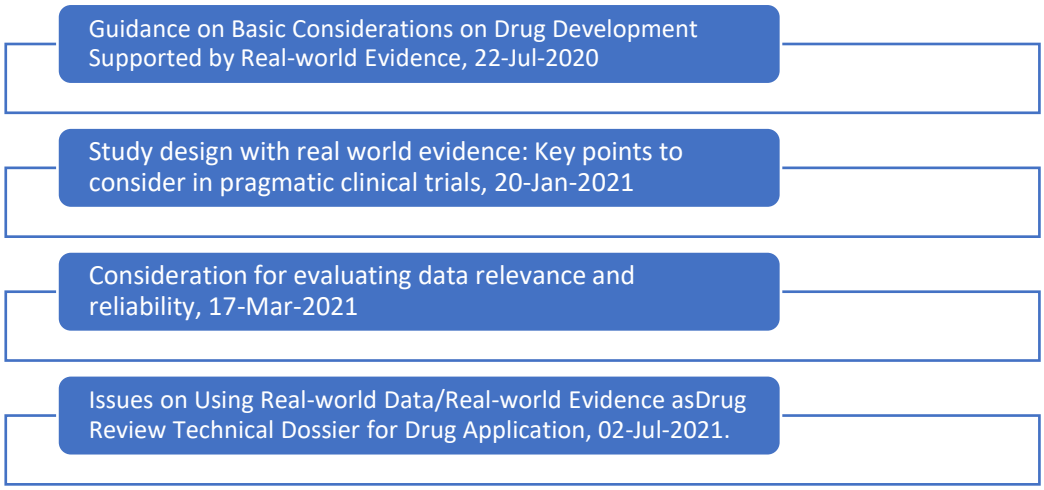

Figure 3. TFDA's guidelines and announcements on RWE

3.6 Switzerland

Swiss medic, the health authority responsible for registering and evaluating pharmaceutical products in Switzerland, operates in accordance with the relevant laws that require the inclusion of clinical trial results in marketing authorization documentation (Article 11, Paragraph 2, Letter a, Number 2 of the Therapeutic Products Act). Swiss medic provides detailed information on the documentation requirements (Article 11, Paragraph 4 of the Therapeutic Products Act). According to Article 5, Paragraph 1 of the Ordinance on the Licensing Requirements for Therapeutic Products (TPLRO), clinical trial documentation must demonstrate compliance with good clinical practice (ICH GCP) guidelines. Real-world evidence (RWE) is accepted as supplementary evidence alongside data from clinical trials conducted in accordance with ICH GCP under the current legal framework. Submissions must comply with the most recent scientific and technological developments. Swiss medic supports to the greatest extent possible the integration of new scientific approaches and technologies in the field of therapeutic products. Given the inherent uncertainties associated with RWE, the existing regulations on acceptable clinical documentation, and the rapidly evolving development landscape, it is advisable to hold a pre-submission meeting with Swiss medic to discuss the appropriate use of RWE before submitting an application.

Swiss medic recognizes RWE as a complement to clinical trial data. For example, the use of appropriate control groups based on high-quality, adequately sized, and relevant real-world data can provide context and support for the clinical trial evidence regarding the efficacy and safety of a specific drug. However, marketing authorization applications solely based on RWE are currently not accepted, as the legal, scientific, and regulatory frameworks for such applications have not yet been established. Adequate clinical trial data remain a minimum requirement for new marketing authorization applications, even when applying a new therapeutic principle within a controlled ICH GCP setting, even in the absence of a control study arm. In the case of variation applications that expand the therapeutic scope, exceptions must be discussed with Swiss medic prior to regulatory submission.

Swiss medic accepts the use of RWE in the context of post-marketing surveillance for the implementation of or changes to risk minimization measures. RWE can therefore be used to include new safety or efficacy information in materials for healthcare professionals or to make other post-marketing changes that modify the therapeutic use of a medicinal product. Electronic health data records and registry data can serve as additional sources for signal detection, evaluation of risk minimization measures, and generation of standard safety reports that may include RWE. (21,22)

3.7 South Korea

Clinical trials conducted in South Korea must adhere to safe and scientifically rigorous methods in accordance with the approved clinical study protocol or its amendments by the Ministry of Food and Drug Safety (MFDS). The MFDS has established many types of clinical trials, such as clinical pharmacology studies, therapeutic explanatory studies, therapeutic confirmatory studies, and therapeutic use studies. Certain trials, however, are exempt from MFDS approval, as outlined in Article 34, paragraph 2. These exemptions include trials conducted to observe the clinical effects of approved drugs, trials for collecting safety and efficacy data on already approved drugs, trials using drugs to develop treatment methods for life-threatening conditions like terminal cancer or AIDS when existing therapies are inadequate, trials involving quasi-drugs, and other cases unrelated to safety or ethical concerns as determined by the MFDS. (23,24)

The MFDS has been incorporating real-world evidence (RWE) into regulatory decision-making; however, a regulatory framework for its handling has not yet been established. The MFDS has not provided specific communication regarding their stance on using RWE for

decision-making in clinical research. Currently, the MFDS focuses primarily on evaluating safety profiles using RWE as part of its post-market surveillance activities. They have developed a comprehensive roadmap for the gradual expansion and implementation of RWE utilization. (25,26) For instance:

The revision of Guideline Guide-0020-06: Guideline on Risk Management Plan (RMP) in December 2020 now allows for RWE/RWD studies to be considered in the RMP.

Guide-1128-01: Guidelines for Research on Medical Information Databases, published on June 29, 2021, provides guidance on utilizing RWE derived from analyzed real-world data, such as national health insurance data and electronic medical records, for post-marketing safety studies.

Insights into the regulatory landscape related to the use of RWE/RWD can also be obtained from publications by the Ministry of Health and Welfare, such as the Health and Medical Data Utilization Guidelines. (27,28)

3.6 Russia

The Russian Ministry of Health passed legislation allowing RWE to register drugs under Federal Law No. 258-FZ of July 31, 2020 "On Experimental Legal Regimes for Digital Innovation in the Russian Federation." (29)

3.7 Other countries and health authority

The following health authorities and countries were also evaluated as part of the Research, and there are no specific recommendations or adoptions by local health authorities for registering drug products based on RWE:

- Federal Institute for Drugs and Medical Devices, **Germany**
- Regulation of the Head of National Agency of Drug and Food Control, **Indonesia**
- Health Research Ethics Board, (PHREB) **Philippines**
- Turkish Pharmaceuticals and Medical Devices Institution (TITCK) **Turkey** (30)
- Ministry of Health of **Ukraine** (31)
- the Scientific Ethics Evaluation Committee / Comité de EvaluaciónÉticoCientífico (CEEC) **Chile** (32)
- National Administration ofDrugs, Food and Medical Technology (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica) – ANMAT **Argentina** (33)

4. Adoption in Commercial/industry

4.1 Role of RWE in treatment and reimbursement decisions

The role of RWE in treatment decisions has become more prevalent in the last five years as a result of increased availability and utilisation of RWD, the growing importance of value-based assessments, and the increased sophistication and breadth of RWE use. While the United States has been slow to adopt RWE, global RWD adoption for Health Technology Assessments (HTAs) has paved the way for its wider use in treatment and regulatory approval decisions. (34,35) The commercial adoption of RWE and the use of RWD in the United States is contingent on payer adoption and acceptance of these data sources and outcomes. (36)

Despite the fact that payer adoption of RWE data for reimbursement decisions has increased over the past two to three years, obstacles remain. The most prevalent difficulty is the applicability of real-world datasets used for analysis. Payers are increasingly expecting their patient populations to be reflected in the real-world datasets used to analyse RWD for relevant products. In addition to RCTs, payers may place less emphasis on discrete choice experiments (DCEs) and patient-reported outcome (PRO) studies. (37,38)

4.2 Impact of Covid-19 on use of RWE

The regulatory trend to grant accelerated approval for products relatively early in clinical trials has been propelled to the forefront by the accelerated approval of Covid-19 vaccines. This trend may be capitalised on by supplementing RCTs with well-defined RWE studies and thereby potentially accelerating the time to market for therapies addressing the greatest unmet needs. (39,40)

Ways in which RWE can support fast track go-to-market approach

- Support the understanding of diseases and unmet needs
- Reduce clinical development cycle time and costs
- Support pricing and demonstrate value
- Improve commercial spending and effectiveness
- Support pharmacovigilance and label extension

To be in the best position to leverage RWE for commercial success, pharmaceutical companies should prioritise their assets, use RWE to complement regular studies for key therapeutic areas with a specific purpose in mind, such as label extension, and use the cleanest data source possible when conducting RWE studies. (41,42)

To further improve their RWE capabilities, businesses must leverage advanced analytics capabilities of the next generation, which are frequently supported by machine-learning specialists who can develop highly predictive algorithms to identify RWD gaps and isolate relevant data fragments while maintaining an audit trail. These capabilities can be employed for both the generation and validation of hypotheses. One specific and extremely valuable application of these capabilities is their capacity to facilitate a more comprehensive comparison of head-to-head studies across multiple clinical endpoints, therapies, and patient groups (43,44) Another application of RWE data that has recently been implemented is pharmacovigilance. RWD from the AstraZeneca COVID vaccine was used in this manner to identify the incidence of blood clots in a small percentage of patients, and the company used this safety signal to update the vaccine's

risk assessment as part of its regulatory submission to the EMA. (45-47)

A more recent use of Real-world evidence has been to make a case for switching from the bio-originator to biosimilar. Multiple studies conducted in adalimumab which is expected to go off-patent in 2023 in the US. These studies compared the originator product to biosimilar versions for primarily rheumatologic indications and conclusively demonstrated that biosimilars have similar efficacy and adverse event profiles, allowing switching discussions to take place. (48,49)

5. Data Source and Quality Measures

The selection of appropriate data sources, as well as the implementation of stringent quality controls, are critical components in the generation of robust real-world evidence (RWE). To begin with, ensuring the representativeness of the data sources is critical in order to capture the diverse patient population and avoid biases. The data should cover a wide range of demographics, clinical characteristics, and healthcare settings so that the findings can be applied to a larger patient population.

The selection of appropriate data sources, as well as the implementation of stringent quality controls, are critical components in the generation of robust real-world evidence (RWE). First and foremost, ensuring representativeness of the data sources is critical in order to capture the diverse patient population and avoid biases. The data should cover a wide range of demographics, clinical characteristics, and healthcare settings, enabling the findings to be applicable to a broader patient population. (50,51) Accuracy and completeness of the data are of utmost importance to establish the reliability and validity of the RWE. (52,53) Robust data validation processes and adherence to data quality standards are essential for identifying and correcting errors or inconsistencies, thereby enhancing the overall quality of the evidence. Standardization of data across multiple sources facilitates data integration and comparison, allowing for effective analysis and interpretation of RWE. In addition, adherence to data governance frameworks, privacy regulations, and ethical guidelines ensures the protection of patient confidentiality and fosters stakeholder confidence. Validation and verification processes, along with transparent reporting and documentation of data sources and quality measures, contribute to the reproducibility and critical evaluation of RWE studies. (54,55)

The table below describes the data source and quality considerations used by various health authorities.

Table 4. Data source and quality considerations used by various health authorities

Regulatory Agency	Data Sources	Quality Considerations
USFDA	EHRs, claims databases, registries, patient-generated data, etc.	Data standards, validation, completeness checks
EMA	EHRs, claims databases, registries, etc.	Fit-for-purpose data, quality assessment, transparency
Japan PMDA	Claims databases, health insurance databases, electronic medical records, etc.	Data accuracy, completeness, traceability
Health Canada	Provincial health administrative databases, electronic medical records, etc.	Data accuracy, completeness, data governance
Taiwan FDA	National Health Insurance Research Database (NHIRD), disease registries, etc.	Standardized data, validation, rigorous study design
Swissmedic	EHRs, claims databases, disease registries, etc.	Data quality standards, validation, transparency
MFDS (South Korea)	Electronic health records, claims databases, disease registries etc.	Data quality assurance,

6. Conclusion

The article discusses the contribution of real-world evidence (RWE) to the field of regulatory development, adoption, and persistence among global health authorities. In addition, it provides valuable insight into the evolving RWE landscape and its incorporation into regulatory decision-making processes.

The findings presented in this article highlight the growing recognition of RWE's significance in shaping public health policies and improving patient outcomes. The adoption of RWE by global health authorities has the potential to transform regulatory frameworks, allowing for a more comprehensive evaluation of the safety, efficacy, and effectiveness of medical interventions.

The perseverance of the regulatory agencies in overcoming challenges related to data quality, standardization, and privacy concerns is commendable and paves the way for the broader acceptance and utilization of RWE in future. The collaborative approach between regulatory authorities, industry leaders, academic researchers, and patient advocacy groups is crucial in advancing the integration of RWE into regulatory decision-making. Such partnerships facilitate the development of standardized guidelines, frameworks, and best practices, ensuring the transparency, reliability, and reproducibility of RWE studies.

In conclusion, this article not only provides a comprehensive overview of the regulatory development and adoption of RWE but also highlights the ongoing efforts to overcome barriers and challenges in its implementation. Hence, will serve as a valuable resource for policymakers, regulators, healthcare professionals, and researchers, fostering a better understanding of RWE's potential to inform evidence-based decision making and ultimately improve global health outcomes.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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