A brief report of real-world evidence development (RWD/RWE) in 2021: United States, Russia, and the Eurasian Economic Union (EAEU)

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Abstract

The article provides a brief overview of the main trends in the development of real-world data and real-world evidence (RWD/RWE) paradigm in the United States, Russia, and the Eurasian Economic Union (EAEU) in 2021. The review is compiled in calendar sequence. First, events in the United States are presented, sourced from the information resource, "The Evidence Base". Following this, data for the Russian Federation and the EAEU are collected and stored on the "myRWD — Real Clinical Practice" Facebook page, and in the journal "Real-World Data & Evidence". The information is summarized and a complete picture of the development of real clinical practice and its evidence in the indicated countries is given.

Keywords: real-world data; real-world evidence; RWD; RWE; USA; Russia; Eurasian Economic Union

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In 2021, the US FDA was tasked with developing clear evidence standards based on real-world data and evidence, RWD/RWE. Since the first Drug Act of the 21st century, many experts around the world have wondered how RWD/RWE will push the boundaries of clinical research. At the end of 2021, the FDA planned to publish a draft guideline for RWD. In particular, this guide will summarize the lessons of the past year using RWE-related applications filed with the FDA or RWE-related product demonstrations conducted by the FDA itself. at the end of the year, the FDA made it clear that RWE had several aspects that needed to be carefully monitored, but that it was possible and useful for the future regulation in medicine.

The FDA RCT DUPLICATE demonstration trial was designed to mimic randomized controlled trials (RCTs) using RWE. The FDA's initial findings were published in January 2021 following ten RWE studies in cardiology [1]. The results showed that six studies met the normative findings expected from RCTs. The results represent a positive start to the year for RWE's reputation with the FDA.

In January 2021, the US also saw changes to how RWE should be handled and reported. The STaRT-RWE template has been introduced for both reporting and implementation of RWE when making treatment decisions [2]. The guidelines have eliminated common pitfalls in dealing with RWE, including lack of transparency in reporting RWE, vagueness that can confuse readers, and introduced a methodology that ensures scientific rigor, including reproducibility, validity, and comparison of evidence. The template can improve important aspects of RWE required by the FDA, such as unambiguous communication of proposed scientific decisions and clarity to a level of reproducibility for effective credibility assessment.

In the EAEU, at the site of the Department for Coordination of Works in the Sphere of Circulation of Medicines and Medical Devices of the Department for Technical Regulation and Accreditation of the Eurasian Economic Commission, a survey of the EAEU member countries was conducted, consisting of 11 questions:

1. Is there a definition of the term "real clinical practice data" and/or the term "evidence obtained on the basis of real clinical practice data" (similar terms) fixed at the level of regulatory legal acts in this EAEU member country?
2. Are there any approaches developed at the level of concepts, strategies or methodological recommendations in this country – a member of the EAEU to use data from real clinical practice and/or evidence obtained on the basis of analysis of data from real clinical practice in decision-making by healthcare organizers (similar to the Framework of FDA's Real-World Evidence Program FDA)?
3. Does this EAEU Member State have specific regulatory approaches regarding cross-border transfer of data/acceptability of sources of real clinical practice data and/or evidence derived from the analysis of real

clinical practice data obtained within other countries of the world or other member countries? EAEU?

4. Are there specific regulatory approaches in this EAEU member country regarding the introduction of real clinical practice data and/or evidence obtained from the analysis of real clinical practice data as part of the scientific rationale or part of the scientific rationale when updating data on the safety and efficacy of medicinal products? drugs/new drug registrations?
5. Are there special approaches in this EAEU member country regarding the use of real clinical practice data and/or evidence obtained based on the analysis of real clinical practice data in conducting post-registration clinical trials and/or in organizing pharmacovigilance (similar to the Framework for FDA's Real-World Evidence Program)?
6. Are there specialized patient registries in this EAEU member country? How is the data contained in such registers used (for the purposes of planning the volume of medical care and / or the need for medicines, medical devices; for tracking the characteristics of the therapy used and using it in the formation of clinical recommendations, etc.)?
7. Does this EAEU member country have special regulatory approaches to the collection and use of human health data generated by medical devices and/or mobile applications?
8. Are there separate approaches at the level of national regulation regarding the classification of software as medical devices?
9. Are there special regulatory approaches in this EAEU member country regarding the possibility of considering real customer data?
10. Clinical practice and/or evidence derived from the analysis of real clinical practice data when developing clinical guidelines?
11. Are there any special regulatory approaches in this EAEU member country regarding the possibility of considering data from real clinical practice and/or evidence obtained on the basis of analysis of real clinical practice data when compiling lists of medicines and/or medical devices to provide citizens free of charge for budget account and/or for public procurement purposes?
12. Are there special regulatory approaches in this EAEU member country regarding medical information systems (including laboratory, radiological, etc.) used in healthcare, as well as the principles and methods for collecting, storing and transmitting data contained in such systems?

In February 2021, the "vaccine race" began around the world. Critical to the global vaccination program, RWE was originally pre-printed in February 2021 and then published in the August issue of Med. A real-world study found that the efficacy of the two vaccine brands was boosted by RWE following their FDA approval. The now-famous Pfizer/BioNTech and Moderna vaccines reduce hospitalizations following COVID-19 infection [3]. Critical to this study were real-world databases that were used to understand how pre-approved vaccines affected a retrospective cohort of 136,532 people. The broader impact of the RWE research is unquantifiable given that these initial studies generated the confidence needed for successful vaccination programs.

Meanwhile, the value of RWE has been explored through additional research led by the FDA. One of them, the Post COVIDity project, was launched to determine how the pandemic has affected various aspects of cancer care, including active treatment, post-treatment outcomes, treatment choice, and more [4]. The project used RWD to provide doctors and patients with useful knowledge about the impact of the pandemic on daily care and treatment. To match relevant RWEs for the study, the FDA has partnered with the Reagan-Udall Foundation (under the FDA) and Friends of Cancer Research (USA) to develop a COVID-19 evidence accelerator. Since its launch in April 2020, this project has generated interest from many stakeholders due to its focus on matching high-quality RWEs on behalf of the FDA [5].

Based on the results of a survey of the EAEU member countries, as well as an analysis of Russian legislation, the Trubor Law Office published the following key regulatory gaps and tasks in the Russian Federation:

- The redundancy of the current regulation for observational studies without intervention in the treatment process. The lack of clear normative links between the results of such studies and the subsequent possibilities of taking the results into account when making decisions on drug provision.
- The statutory patient registries focus on demand planning and are closed systems. There is no focus on collecting and analyzing data from real clinical practice.
- The pharmacovigilance system in the form of messages (the order/form is adjusted) receives data from real clinical practice (the list is defined). The information is undergoing an examination, the results of which affect the circulation of medicines. The system is closed → limited RWD/RWE segment.
- The current legal field does not exclude the possibility of using data from real clinical practice in the development and revision of clinical guidelines. There are scales for assessing the reliability of evidence → discussions are needed, which is required additionally; there is a framework for collecting patient health data that is generated by medical devices as part of medical surveillance. There is no special procedure for the subsequent processing and use of the relevant data. Additionally, a link with clinical guidelines is needed.

In March 2021, the FDA made additional RWE and RWD disclosures for submission to medical device regulatory authorities [6]. Such guidance seemed necessary given the growing amount of RWD generated by non-medical wearables, including the various smartwatches currently in existence or measurement applications. When creating an RWE with these tools, as suggested by the FDA, the safety and efficacy of existing devices should be studied before they take on new functions. The FDA has praised new and future medical devices for their ability to generate original RWDs. Subsequently, information registers collected from both pre-existing and new technologies were considered excellent opportunity both for creating high-quality RWEs and for constantly monitoring duties of the FDA. A summary document was released detailing examples of submitted RWE-enabled products that were subsequently approved by the FDA [7].

In March 2021 in Russia on the basis of the Center for Strategic Research (CSR) as part of the conference "Lessons of the COVID-19 pandemic. Opportunities for Improving the Efficiency and Sustainability of the Healthcare System" a round table was held on the topic "Collection and analysis of clinical practice data in the context of the COVID-19 pandemic: place in the healthcare system and implementation problems".

In Europe, in April 2021, a new institute was formed to study the use of RWE in healthcare, called the GetReal Institute (Netherlands) [8]. The purpose of this new non-profit organization is multifaceted: it builds solidarity around the understanding and importance of RWE; overcoming common problems that arise when using RWE; to be a trusted source of RWE knowledge and training, and to provide a common basis for all RWE initiatives in Europe. Coinciding with the launch of the event, NICE (UK) joined the organization as a founding member along with nine other European organizations [9]. Interest in institutions like the GetReal Institute has highlighted the goal of European regulators to use RWE for regulatory decision making, like the FDA in the US.

In April 2021, in Russia, within the framework of the VIII All-Russian Conference with international participation "Actual issues of preclinical and clinical studies of drugs, biomedical cell products and clinical trials of medical devices", a symposium "RWD/RWE: from glossary to applicability" was held. Later, within the framework of the 8th Interregional Scientific and Practical Symposium with international participation "Pharmacoeconomics of Viral Infections", the outcomes of COVID-19 treatment were discussed: evidence-based medicine vs real clinical practice.

In early May 2021, well-known industry leaders in the US including Aetion (New York, USA), Flatiron Health (New York, USA), IQVIA (North Carolina, USA), Syapse (California, USA) and Tempus (Illinois), USA), formed a new coalition (Alliance) Alliance RWE (Maryland, USA) [10]. The group is committed to supporting the use of RWE for FDA regulatory decisions. To do this, the Alliance has offered to partner with several stakeholders who have invested in RWE, including patient groups, biopharmaceutical companies, and others. Collaboration in these areas is expected to provide comprehensive evidence that can be used for regulatory decision making. Most importantly, the RWE Alliance intended to provide feedback on the important RWE guidance developed by the FDA, due to release in December 2021.

In June 2021, the RWE Alliance delved into discussions about Cures 2.0. The inclusion of various health policies has been praised as the adoption of a broader approach to health care is expected to improve patient outcomes. Central to the RWE Alliance's comments on the guidance was that "RWD and RWE play a critical role in informing decisions about the registration and use of medical devices". The idea that RWD can inform decisions is especially relevant to COVID-19, when RWE has been used to treat infected people and better understand the spread of the disease. Thus, incorporating different health care policies can ensure that RWE is used to the maximum in situations where it is appropriate to achieve the best patient outcomes. Concerning future recommendations, the RWE Alliance believes that the next steps taken by the FDA should include defining and implementing the FDA's RWE Framework.

In Russia, the role of RWD/RWE in terms of healthcare digitalization is being actively discussed. So, in the Public Chamber within the framework of the conference "Digitalization of healthcare. The view from the side of the patient community" was held the seminar "Collection of RWD/RWE" [21]. Clinical pharmacologists pay active attention to the role of RWD. In May 2021, within the framework of the XII All-Russian scientific and practical conference with international participation "Actual issues of clinical pharmacology and drug provision", a discussion was held on the topic "RWD/RWE. The current state of the problem in the aspect of COVID-19".

In July 2021, the FDA approved the first RWE-based drug as tacrolimus received a new prescription due to RWE research. Starting with the treatment of rejection after liver transplantation, tacrolimus (brand name Prograf®) was later used for kidney and heart transplants. This year, however, the drug's potential has expanded even further, including lung transplantation, with the help of the FDA-approved RWE study. The Regulator has recognized that when non-interventional studies are carefully designed and include appropriate RWDs, the input is very helpful [11]. While data from clinical trials have been shared with RWE to persuade the FDA to approve tacrolimus, the result was certainly welcome. It was noted that having strong and valuable RWE registries helps make this claim, which is important in determining how best to handle RWD in the future. As we all know,

the importance of RWE lies in assessing the effectiveness of treatments in clinical practice, since RCTs cannot consider all circumstances. However, the news that RWD results from clinical trials of pertuzumab and trastuzumab emtansine in metastatic breast cancer shocked everyone. Serious consequences arose under RWE, as survival rates were lower than in clinical studies. However, understanding how prior treatment can affect actual outcomes is an important finding that can be transferred to various medical fields. Further discussions focused on how to improve the drug review process, including the use of RWE. As part of a much broader and more regular FDA review process, the Prescription Drug Consumer Act – PDUFA VIII – has been evaluated against the current usage and re-approved under new and improved terms. Recommendations made during the discussion were aimed at improving the development of drugs for rare diseases and updating the procedures for validation studies. Along with this, it was proposed to conduct a pilot study on how the FDA can practically use RWE [12]. This meant that this ongoing work by the FDA to ensure that RWE could be implemented in regulatory decisions was of great importance.

In June 2021, in Russia, as part of the VI conference "Digital Industry of Industrial Russia", a session "Digital Health in the Post-Covid Era" was held, a symposium "RWD/RWE in the aspect of digitalization of healthcare" was held [22]. Later, at the Interregional Scientific and Practical Conference "July Dews: Refreshing Seminar for Clinical Pharmacologists", pharmacovigilance, and RWD was discussed.

Of course, digitalization is the most important tool for obtaining RWD. Thus, in the United States, a draft guide was released on the use of RWD sources, including electronic health records (EMRs) and medical claims [13]. These RWD sources will be used in the RWE study to highlight the efficacy and safety of a particular treatment. The submitted draft guidance is open to comments from biopharmaceutical companies to better understand how these types of RWDs can help guide regulatory decisions.

In August 2021, at the site of the department for coordinating work in the field of circulation of medicines and medical devices of the Department for Technical Regulation and Accreditation of the Eurasian Economic Commission, changes to the legal framework of the EAEU were proposed. In the Rules for registration and examination of medicinal products for medical use, approved. Changes were made by the decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 78 (hereinafter the Registration Rules). First, in Section II "Definitions" of the Registration Rules, the terms "real clinical practice data" and "evidence obtained on the basis of real clinical practice data" are given. The term “real clinical practice data” can be defined as “data relating to the health status of the patient and/or the process of providing medical care, obtained from various sources". The term "real-world evidence" can be defined as "clinical evidence regarding the use and potential benefit or risk of a medicinal product based on the collection and analysis of real clinical practice data". Paragraph 148 of the Registration Rules is worded as follows: "The holder of the registration certificate must inform the authorized body of the Member State about all new information that may require changes in the documents and data contained in the registration dossier of the medicinal product. The marketing authorization holder must immediately notify the authorized body of the Member State of any prohibition or restriction of the medical use of the medicinal product imposed by the authorized bodies of any state on the market of which the medicinal product is located, and of all other information that may affect the assessment of the ratio of "risk-benefit" of the medicinal product in question. The information should include both positive and negative results of clinical trials or other studies (including those containing evidence obtained on the basis of data from real clinical practice) for all indications and in all groups of patients, regardless of whether they are included in the registration dossier, as well as data on the use of the medicinal product, if such use does not meet the conditions of registration.

Also, in the Rules of Good Pharmacovigilance Practice of the EAEU, approved. By the decision of the Council of the Eurasian Economic Commission dated November 3, 2016 No. 87 (hereinafter the Rules of Pharmacovigilance), changes were made to the terminology of the Rules of Pharmacovigilance to clarify that: "post-authorization safety study (PASS) — a study related to a registered medicinal product, conducted to determine, characterize or quantify a safety hazard, confirm the safety profile of a medicinal product, or evaluate the effectiveness of risk management measures. PASS may be an interventional clinical trial or may be conducted as an observational non-interventional design study, including using real clinical practice data".

It should also be noted that it was proposed to develop a concept (strategy) for developing the legal framework of the EAEU in terms of regulating the collection, analysis and use of data from real clinical practice and evidence obtained on the basis of data from real clinical practice, by analogy with the "Basics for the RWE program FDA" (Framework for FDA's Real-World Evidence Program).

In Russia, on September 16, 2021, the Association of Specialists in the Field of Health Technology Assessment, the Association of Clinical Pharmacologists, provide the conference "Research tools for real clinical practice today and tomorrow" [23]. As part of the plenary session, panel discussion and practical experience discussion session, Russian and international experts in the field of RWD/RWE spoke, leading Russian clinicians discussed practical issues of working with RWD/RWE, and the

position of business, holders of registration certificates was presented. The conference participants discussed real clinical practice research tools, the growing importance of RWE in modern medicine, legislation, as well as global perspectives in the world and Russia. And, of course, we separately discussed technological changes during the COVID period. In total, 30 reports were heard at the conference, and a resolution [19] was developed and approved. Later, RWD/RWE was discussed at the II Forum of Patient-Centred Innovations, organized by the All-Russian Union of Patients.

October 2021 showed an active effort to improve the credibility of RWE research. As part of a collaboration between ISPOR, the International Society for Pharmacoepidemiology, the Duke-Margolis Center for Health Policy (USA), and the National Pharmaceutical Council (London, UK), a Real Evidence Register was launched [14]. The registry complements the work of the Real-World Transparency Initiative, which is made up of these collaborating societies. The advantages of the RWE listed on the Registry include the cost-effectiveness of getting RWD quickly and the lack of patient representation in RCTs. Since the Registry is hosted in the public domain, researchers will be able to increase the transparency of their research while obtaining the necessary RWD.

In the US, October 2021 saw RWE peaking to help more patients as researchers used RWD to repurpose the FDA-approved Alzheimer's drug bumetanide. A Nature Aging paper published online in October 2021 highlights the benefits of using different RWD sources [15]. These sources included databases containing genetic information about the brain, originally used to understand the genetic transcriptome features of Alzheimer's disease. After that, another valuable source of RWD, containing FDA-approved treatments, helped create the RWE on how treatments affect people in the real world, including variables such as age and other genetic information. EHRs have demonstrated that in individuals at genetic risk of Alzheimer's disease, the administration of bumetanide reduces the progression of the disease.

In October, within the framework of the International Congress "Information Technologies in Medicine", a symposium "RWD/RWE: synthesis of real data for decision making" was held in Russia. Later, at the III International Conference "The Life Path of Medicines: Simple and Complex Problems", the topic "RWE. What's next? Examples of tools for decision-making".

In November, the American Society for Clinical Pharmacology and Therapeutics released a paper highlighting the intention of the European Medicines Regulatory Network (EMRN; Amsterdam, The Netherlands) to include RWE in its regulatory processes. The outlook, published in November 2021, highlights previous work already done by the European Medicines Agency (EMA) to involve RWE in regulatory decision-making [16]. This includes an approved plan to develop an RWD network available to EU members called the Real-World Data Analysis and Inquiry Network (DARWIN EU). Although the project is planned for 2022, funding sources and stakeholders were identified during the year. In any case, this document certainly paves the way for RWE in the future decisions of the European regulator. The FDA has created additional elements of the RWE Framework. This time the guide is based on the October version and includes registries [17]. Specific information is included on when the FDA deems an RWE registry appropriate, as well as how to link RWD data sources, including EHRs and others, to registries. Expanding the definition of RWE sources that can be submitted to the FDA is critical to its implementation in regulatory decisions, given the many sources of RWD that can be collected. Similarly, the data that can be collected through each respective RWD source is subject to variation, potentially meaning that the FDA could require the RWE to be able to make an informed regulatory decision based on it.

At the site of the Civic Chamber of Russia, within the framework of the conference "Personalized Medicine: Focus on the Patient", the prospects for introducing RWD/RWE data in the Russian Federation were discussed. Then the topic of RWD was discussed at the forum "Clinical Research in Russia 2021", the theme of the symposium was "RWD/RWE in the world and the EAEU. Background, current status, problems, and prospects". Later, at the XXV Russian Cancer Congress, a symposium "Pharmacoeconomics in Oncology" was held, because of which a resolution was developed and approved [20].

In 2021, the bilingual peer-reviewed journal "**Real-World Data & Evidence**" began to be published in Russia, which publishes original studies and reviews on the use of data obtained in routine medical practice to assess outcomes treatment and health decision making. Articles published in the journal cover, but are not limited to, such key areas of scientific research as the use of patient and nosology registries, medical databases, electronic medical records, drug consumption, study of treatment outcomes in real clinical practice, analysis of prescriptions in inpatient and outpatient settings, drug safety, adherence to treatment, comparative efficacy studies, clinical economic analysis, including analysis of the cost of disease and burden of disease, pragmatic clinical trials and large simplified randomized trials, the study of research methodology based on real clinical practice data, including collection, tracking, search, sharing, analysis and interpretation of "big data". The journal's website http://MyRWD.ru/ also publishes news on real clinical practice studies, conferences, congresses and other events. The journal "**Real-World Data & Evidence**" has an online publication system: after the work on the manuscript is completed, it is published on the journal's website as soon as possible with the assignment of DOI to it. After online publica-

tion, it is impossible to make changes to the manuscript. Once every six months, all manuscripts published on the site during this period are combined into an issue. Before the formation of the release, the authors can print the articles published on the site, while the generated files contain the necessary output data.

In December 2021, the RWE FDA Framework Level 1 guidance was released in the United States [18]. The guidance itself covers four broad areas that require attention when using RWE: transparency of the methodology; data access and privacy; study monitoring; responsible safety reporting and guidance for sponsors. It is hoped that with this guidance, the quality of RWE research will be maximized for submission to the FDA and therefore may impact the medical field under consideration. Since the goal of the FDA is to provide an improved development lifecycle for patients in need of treatment, this guidance is one big step in the right direction.

On December 3, 2021 in Russia, within the framework of the seminar "Cochrane Systematic Reviews: Reliable Evidence for Wise Decisions in Medical Education, Science and Practice" [24], the unique role of Cochrane Systematic Reviews in the translation of reliable evidence, including in RWD/RWE, was demonstrated. MyRWD

ADDITIONAL INFORMATION

Conflict of interest. The authors declare no conflict of interest.

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23. 16 сентября состоялась II Ежегодная научно-практическая конференция с международным участием «RWD/RWE — инструменты исследования реальной клинической практики: сегодня и завтра». Режим доступа: https://aston-health.com/about-us/press-center/news/16-sentyabrya-sostoyalas-ii-ezhegodnaya-nauchno-prakticheskaya-konferenczi-ya-s-mezhdunarodnyim-uchastiem-%C2%ABrwd/rwe-instrumentyi-issledovaniya-realnoj-klinicheskoj-praktiki-segodnya-i-zavtra%C2%BB/. [On September 16 took place the II Annual scientific and practical conference with international participation "RWD/RWE – research tools for real clinical practice: today and tomorrow". (In Rus.)]
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