Real-world data: general regulatory approaches in the EU and Japan

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Abstract

The article describes the regulatory approaches to the collection, analysis and usage of real-world data applied in the European Union and Japan.

Keywords: real-world data; regulatory approaches; international experience

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Introduction

Real-world data (RWD) is a legal institution that began its formation in developed legal systems. In the United States, the European Union (EU) and Japan, pilot projects are being launched, working groups are being created to discuss the most pressing issues in this area, and a change in the regulatory framework is being worked out. The study of relevant experience is necessary, among other things, to assess the possibilities of borrowing and adapting existing international practice approaches to the law of the Eurasian Economic Union (EAEU) to improve the quality and accessibility of medical care for patients.

Materials and methods

Analysis of international regulatory experience is a complex task. On the one hand, there is a fundamental difference between the legal traditions that exist in the Anglo-American and Romano-Germanic systems of law. On the other hand, globalization has led to a convergence of the approaches of these two systems, and the creation of supranational state formations and the emergence of union law (in particular, in the EU) has led to an alignment of various legal and regulatory principles. In this regard, the analysis of international experience is impossible without tracing the history of the formation of certain instruments in law. In addition, when analyzing foreign regulatory experience, a fundamental role is played by the doctrine and interpretations of experts, which, among other things, were used to prepare this article.

Results

This study showed that the basic approaches to regulating the collection, analysis and use of data from RWD are contained not only in practical guidelines, but, first of all, are laid down in the high-level strategic documents existing within developed legal systems that set the vector for the development of RWD related legal field for the medium- and long-term perspective.

Analysis of regulatory approaches in the EU

In August 2016, the European Medicines Agency (EMA) published Guidance for companies considering "adaptive pathways" approach for drug entry into the pharmaceutical market (hereinafter referred to as the Adaptive Pathway Selection Guide). [1]. The Adaptive Pathway Selection Guide provides a number of examples of how real-world evidence is used to support regulatory decision making in the EU, including:

i. use of existing disease registries to identify natural history of the disease, current Standard of care, resource utilization, adherence to treatment;
ii. single arm studies for rare diseases compared with outcomes inferred from disease registries;
iii. open label salvage studies in patients with no therapeutic options remaining, with the purpose of obtaining an expansion of the indication;
iv. collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations;
v. post-authorisation drug registries for effectiveness, long-term outcomes, drug utilization, PROs, time to treatment failure, diagnosis confirmation;
vi. linking drug registries to risk-sharing schemes for reimbursement (pay per performance, annuity payments…);

vii. expansion of the indication based on a mixture of disease registries and compassionate use data (for rare, severe diseases, where RCT data were available for less severe forms of the disease);

viii. post-authorisation studies to investigate biomarker (or other subpopulation selection criterion) status of an all-comer population;

ix. investigation of non-serological outcomes for vaccines.

At the same time, the issues of using RWD have also been fixed at the level of strategic documents of the European Union. Thus, on March 31, 2020, the EMA published the Regulatory Science Strategy to 2025 (hereinafter referred to as the Strategy) [2]. Clause 3.3.4 of this document requires that the EU competent authorities "promote use of high-quality real-world data (RWD) in decision-making".

According to the Strategy, RWD are used in the EU predominantly in the post-authorisation phase of the medicines' lifecycle. However, the EMA recognizes that there is greater potential to use real-world clinical data, including to alleviate possible limitations that companies face in conducting clinical trials and to provide additional information on the risk-benefit ratio of medicines. At the same time, the Strategy also indicates the need to create methods for working with sources of information, analytical and epidemiological methods for obtaining reliable evidence, and ensuring the security of information and data.

To fulfill these tasks, EMA offers:

x. to deliver a sustainable platform to access and analyse healthcare data from across the EU;

xi. to conduct a pilot of using rapid analytics of real-world data (including electronic health records) to support decision-making at the Pharmacovigilance Risk Assessment Committee and the Committee for Medicinal Products for Human Use;

xii. review of the utility of using electronic health records for detecting drug safety issues (including drug interactions);

xiii. mapping of good examples of use of RWD in different phases of drug development to develop guidance on such use.

In 2019, a joint Heads of Medicines Agencies and EMA Big Data Task Force Report (further – the Report) was released [3]. Within the framework of ensuring "timely access to pan-European health data", the Report recommends supporting the creation of distributed data networks to improve timely access to information in order to accelerate the real-world evidence generation across multiple datasets. In the area of "data linkage", the Report recommends investing in methods to link pharmacovigilance data sources with other real world clinical and nonclinical data sources. Also within the framework of the "collecting pharmacovigilance data and implementing risk minimization", this Report recommends to continue developing applications for directly gathering data from patients on adverse events and encourage their wider use in real world and study settings.

In 2021, the ninth revision of the Guidelines of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance on Methodological Standards in Pharmacoepidemiology (hereinafter referred to as the Guidelines) was carried out [4]. The Guidelines provide a number of references to methodological standards for the use of RWD in research (including international ones).

In addition, a number of projects have been implemented to explore the possibilities of using RWD in the EU [5], such as:

xiv. IMI ADAPT SMART Project, which assessed the use of RWD to complement randomized clinical trials (RCT) data and provide sufficient evidence to either expand an existing indication to other patient subgroups, or support the addition of a new indication;

xv. IMI GetReal and GetReal Initiative Projects (2013-2021 годы). IMI is a public-private partnership between the EU and the European pharmaceutical industry (represented by the EFPIA) that collaborates on a range of initiatives aimed to advance and accelerate patient access to medicines, particularly where there is unmet need. The GetReal projects discussed, proposed, and created tools to support new robust methods of RWE synthesis for use throughout the drug lifecycle, including regulatory decision-making.

Thus, in the European Union, in fact, RWD has been used to support the decision-making of authorized bodies for a long time. Regulation on this issue is not detailed at the level that exists in the United States of America [6]. However, provisions for the possibility of using RWD are contained both at the level of strategic documents and at the level of more practical guidelines. From this point of view, it is possible to borrow such an approach into the law of the Eurasian Economic Union.

Analysis of Regulatory Approaches in Japan

In 2014, the Pharmaceuticals and Medical Devices Agency of Japan published guidelines for conducting pharmacoepidemiologic drug safety studies based on information contained in medical databases (such as administrative claims database, pharmacy organization database, electronic medical records and care information) [7]. This document is considered in the scientific literature as the first act about the utilization of RWD to assist not only employees of pharmaceutical companies in matters related to planning, conducting and evaluating pharmacoepidemiological studies, but also academic researchers [8].

In 2017, the Ministry of Health, Labor and Welfare of Japan published the document "Basic principles on

utilization of medical information database on pharmacovigilance at post-marketing stage" [9]. In addition, since 2017, the Pharmaceuticals and Medical Devices Agency of Japan has been providing consulting services on the use of RWD in the development and planning of post-registration studies [10]. In 2018, the Pharmaceuticals and Medical Devices Agency of Japan published the document "Points to consider for ensuring the reliability of post-marketing database study for drugs" [11]. In 2019, the Act on Securing Quality, Efficacy, and Safety of Products including Pharmaceuticals and Medical Devices, was amended to clarify the utilization of RWD in pharmaceutical regulation. It stated that academic societies, universities, institutions, and other relevant organizations should make efforts to cooperate in the appropriate use of pharmaceuticals and other medical products, and collect information (including RWD) to ensure the appropriate use of pharmaceuticals and other medical products (including RWD) [12].

Moreover, the updated Japan Revitalization Strategy, adopted in 2015, has become an incentive to introduce new research methods, in particular, by creating a specialized infrastructure based on information contained in disease registries [13]. Referring to the need to use registries, including disease registries and product registries, in drug development in cases where traditional randomized clinical trials are not possible (for example, for orphan drugs), the Pharmaceuticals and Medical Devices Agency in March 2021 developed: "Basic principles on utilization of registry for applications" and "Points to consider for ensuring the reliability in utilization of registry data for applications" [14]. These two guidelines apply when registry data is included in clinical trial documents submitted to a competent authority under the Act on Securing Quality, Efficacy, and Safety of Products including Pharmaceuticals and Medical Devices.

The use of RWD to assess the safety or efficacy of a drug by the authorized body is also allowed under the conditional drug registration procedure introduced in 2017, which was formalized in the Act on Securing Quality, Efficacy, and Safety of Products including Pharmaceuticals and Medical Devices in 2020 [15].

In 2019 and 2020, the Pharmaceuticals and Medical Devices Agency of Japan also initiated consultations targeting the registry data and database-based studies not only for pharmacovigilance but also for new drug applications.

In March 2020, the document "Points to consider for ensuring the reliability of post-marketing database study for regenerative medical products" was prepared. In March 2019, the document "Procedures for Development of Post-Marketing Study Plan" was published [16].

In April 2021, the Japan Pharmaceuticals and Medical Devices Agency (PMDA) established the RWD working group, which comprises multidisciplinary PMDA experts from various offices such as the office of new drug review, pharmacovigilance, nonclinical and clinical compliance, medical informatics, and epidemiology. The RWD working group discusses all regulatory issues related to RWD/RWE, such as data reliability standards and methodological approaches, and promotes utilization of RWD in the Japanese regulatory framework. This group also plays an active role in sharing knowledge and experiences not only within Ministry of Health, Labor and Welfare and Pharmaceuticals and Medical Devices Agency, but also with stakeholders, academia, and foreign regulatory authorities. [17].

Despite the fact that international experts point to the lack of a fixed formal definition of the term "real-world data" in the legal field, Japan has developed approaches to the possibility of using such data to support regulatory decision-making. An analysis of the relevant approaches is also appropriate for assessing a possible borrowing into the law of the EAEU.

Conclusion

Based on the foregoing, it can be concluded that in international experience, approaches to the collection, analysis and use of RWD are actively developing. Nevertheless, even developed legal systems face complex challenges that need to be addressed. Thus, "Study on the use of real-world data (RWD) for research, clinical care, regulatory decision-making, health technology assessment, and policymaking", prepared under the auspices of the European Commission in July 2021 [18], indicates the following main areas of action needed to improve approaches to the collection, analysis and use of RWD in the EU, including:

i. development of common methodological principles for RWD collection and analysis;
ii. support of the accessibility and interoperability of RWD;
iii. ensuring a coherent interpretation and application of the GDPR for the use of RWD;
iv. improving information on and understanding of RWD's scientific integrity, quality and accuracy;
v. development and approval of a comprehensive strategy for the use of RWD in healthcare;
vi. demonstrating RWD's practical relevance through pilot actions;
vii. promoting synergies between existing RWD initiatives and exploiting the work of completed projects.

The recommendations outlined above are relevant not only within the EU, but also for the EAEU, and the corresponding action plan may become the basis for developing approaches to regulating the use of RWD in the EAEU in the future.

ADDITIONAL INFORMATION

Conflict of interest. The author declares no conflicts of interest in connection with this work.
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