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Opportunities for using Real-World Data (RWD) to Generate Real-World Evidence (RWE) in Japan

Contents

Introduction

Real-world data (RWD) held in databases in electronic patient records, medical claims data, and disease registries could generate valuable real-world evidence (RWE) that could offer new insights into diseases, treatments, and new indications for drugs on the market. A new era of precision medicine beckons.[1,2]

Japan is finally, if cautiously, moving toward this exciting future. In March 2021, the Ministry of Health, Labour and Welfare (MHLW) in Japan, issued two guidance documents on "Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications"[3] and "Basic Principles on Utilization of Registry for Applications."[4] These guidance document discuss the application of registry data for generating RWE for orphan drugs treating rare diseases.

This is a promising place to start since the hurdle for regulators to use external, observational data to approve a therapy is lower than in other therapeutic domains. Some patients need the therapy, even when there is no strong evidence from a randomized controlled trial (RCT), says Dr. Osamu Komiyama, Senior Manager, Statistical Research and Data Science Group, Pfizer R&D Japan. "RWD can be an option for building evidence when there are few cases in the country and it may not be possible to conduct RCTs, as in the case of rare diseases."

Another reason for the guidance documents focusing on this narrow area is because databases are not fully developed, says Dr. Toshifumi Sugitani, RWE Lead, Japan Medical Department, Bristol-Myers Squibb K.K. "While regulators [in other countries] provide guidance on the use of real-world electronic medical record data, historical clinical trial data, and medical claims data, the MHLW documents focus on registries because there is a lack of progress in the development of medical databases in Japan (especially electronic medical records and claims data)."

However, the rest of the world is considering other applications of RWE besides those for rare diseases.[2] The US and EU investigators and regulators, for example, discuss how to conduct observational studies to provide evidence that phase 3 studies cannot provide.[1,2]

SECTION 1

Why is the scope to use RWE in Japan so limited in comparison?

Yuji Fujii Senior Client Relationship Director, Enterprise Accounts Japan, Parexel International, says part of the reason is that patient databases in Japan, such as the National Database of Health Insurance Claims and Specific Health Checkups (NDB), are still in their infancy compared to those in Europe and the US."

Other reasons for regulatory authorities only considering RWE within this narrow scope include limited access to patient data, as well as the fact that the data needed may lie in unlinked databases. Furthermore, "if a prospective RCT, including a global clinical trial, can be conducted in the review or re-review for manufacturing and marketing approval, then so much the better. But there is not enough of a scientific argument for using RWE as the next best option when that cannot be implemented," says Dr. Komiyama.

Access to data is another issue. Patient data might not be directly accessible to pharmaceutical companies because the data is not theirs. Governmental bodies, universities, academic societies, and private hospitals are the owners and managers of disease registries, medical claims data, and electronic medical records. Thus, because academia manages the databases, pharma needs to go through the organizations that own the data or get special access rights.

However, the situation is changing. Dr. Yasuyuki Katayama, Associate Vice President, Head of Medical Affairs, Executive Officer, MSD Japan, and Chairman, Pharmaceutical Research and Manufacturers of America (PhRMA) Japan Medical Affairs Committee and Working Group 1 members of the committee are having discussions with MHLW officers on obtaining access to the National Database (NDB), Japan's medical claims database. They have obtained limited access but are continuing discussions with the MHLW to obtain greater access to the data.

Another barrier to the adoption of RWD/RWE is the lack of agreed methodologies for generating evidence from the data.[5] Added to this is pharma's lack of incentive to use new data sources to complement RCTs for new drug approvals, or new indications post-marketing says Dr. Komiyama. "Many in the industry wonder why they have to deal with new data sourczes when they can continue to market their products, protected by the re-examination system."

The question is: will pharmaceutical companies in Japan have enough incentive to use RWD to conduct scientific observational studies to complement RCTs and post-marketing applications?

"It is clear that the Japan guidance documents have limitations, as discussed in a recent paper written on behalf of the committee[5]" says Dr. Katayama, who adds, "I and committee members understand the need to seek harmonization across the globe [through International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)] on standards for evaluating RWD/RWE for regulatory purposes."

In addition, the Pharmaceuticals and Medical Devices Agency (PMDA) – the regulatory body reviewing new drug and device applications, new indications and post-marketing activities – has also reported an increase in inquiries on acceptable methodology for studies using RWD.[6] Formal guidance from the MHLW that reflects these discussions should follow.

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Yasuyuki Katayama Associate Vice President, Head of Medical Affairs, Executive Officer, MSD Japan

SECTION 2

How useful is the guidance?

Regulators describe in the guidance how external, historical observational data from small numbers of patients can be used as a control group for the approval of orphan drugs.[4] An example of external data is US registry data of infants born with the disease before treatment was available. This methodology has been used in the past, though the guidance documents now clarify the documentation requirements.

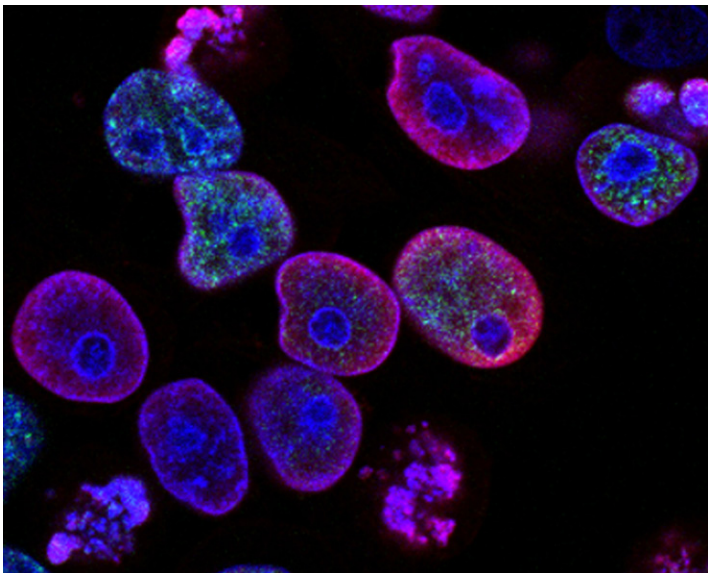
Dr. Komiyama explains, "The use of RWE as an external control has recently been attracting attention, and the ICH E10 Guideline: Choice of control group in clinical trials (Notification by the Director of the Medical and Pharmacovigilance Division, MHLW, Pharmaceutical Affairs Bureau No. 136, 2001) outlines the issues involved in using external controls. In 2001, external controls based on medical information databases were not available in Japan, but the issues discussed in the ICH E10 Guideline have not faded away."

Early studies using RWD for the control came from outside Japan, though recently, disease registries in Japan are being used for the same purpose. Dr. Sugitani explains, "Currently, there are almost no [disease] registries [in Japan] that perfectly fit into the regulatory submissions of pharmaceutical companies." "However, there is an exception," he says. "REMUDY, the registry of muscular dystrophy, owned by the National Center of Neurology and Psychiatry, is used by some pharmaceutical companies for regulatory applications."

Orphan drug status was issued for one therapy for a patient group with a genetic mutation in Duchenne muscular dystrophy in the [REMUDY] registry.[7] The pharmaceutical company can now follow patients in the registry to continuously monitor Japanese patients treated with the drug and report all safety and efficacy data.

All the experts interviewed for this report welcomed the way the guidance document clarifies the requirements for using registry data in the regulatory approval of treatments for rare diseases. "The acceptance of disease registry data as one type of RWD is a significant step in the utilization of RWD," says Dr. Katayama.

Naotsugu Oyama, Corporate Officer Head, Clinical Development & Analytics Japan, Global Drug Development Division, Novartis Pharma K.K. supports the guidance and agrees that the criteria for data use are more transparent now.



Kanae Togo, Senior Manager, Outcome & Evidence, Health & Value, Pfizer Japan Inc. says, "I think the guidance helps us understand requirements for submitting registry data for regulatory purposes, which will increase somewhat, but mainly for rare diseases."

And Mr. Fujii says that the guidance "is significant for the future development of RWD in Japan in terms of promoting awareness of the data use."

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> **Yuji Fujii** Senior Client Relationship Director, Enterprise Accounts Japan, Parexel International

SECTION 3

Limitations in the use of RWE in Japan

Immaturity of medical databases

Regulators outside Japan are providing more guidance on how to use other data sources besides disease registry data, including electronic medical record data, historical clinical trial data and claims data. Why is this so?

This lack of progress in database development seems central to the issue, Dr. Sugitani explains: "The difference may be related to Japan lagging far behind Western countries in developing medical databases, especially electronic medical records and claims data."

The disease registries might be developed however, Yuji Fujii says, "[Other] patient databases in Japan such as the [National Database of Health Insurance Claims and Specific Health Checkups (NDB)] are still in their infancy compared to those in Europe and the US. Therefore, I suspect that, in reality, there is still a limited amount of patient data available other than registry data for some rare diseases [that can be used in studies]."

Limited access to databases and registries

Another reason is that besides the lack of development in databases, access is limited too. Many valuable disease registries, medical claims, and electronic medical records databases are managed by governmental agencies, academic and medical institutions. However, pharmaceutical companies have not fully utilized them yet because the data might not be shared, or privacy issues exist that do not allow the sharing.

"Pharmaceutical companies are not directly involved in establishing the registries," Dr. Katayama says, "But they collaborate with the registry owners, such as academic societies and medical institutions, to analyse the collected data. In addition, there are various ways to collaborate, such as signing a joint research agreement or obtaining access rights for the pharmaceutical company to analyse the data on its own."

However, "Pharma companies utilize academia-driven registries for post-marketing surveillance, market access, and medical affairs projects," says Dr. Oyama.

In other words, academic institutions partner with pharmaceutical companies, managing post-marketing registry studies to monitor adverse events and efficacy, which is a requirement of the Japanese regulatory body after drug approval.

Another way to utilize a registry or database is to have a contract research organization act as a bridge between academic institutions and pharmaceutical companies to obtain data. "When we receive a request for an RWD/RWE project, we ask each company how they intend to use the data," says Parexel International's Fujii. "For example, suppose patient data for the disease is insufficient to support the analysis. In that case, we collect data as an observational study under contract with the medical institution that owns the patient data."

Pharma's access to data is improving. Dr. Katayama says, "I and others had several exchanges with MHLW officers in charge of the NDB, which had initially limited access to private sectors including pharma companies. Eventually, the act was updated so that private sectors could access the NDB. However, some hurdles remain, so we are still keeping the communication with them to improve access."

Limited linkage of databases and registries

Besides limitations in access, the databases are not linked. "The biggest issue," says Dr. Katayama, "is how to digitize the people's health records and how to link the disparate databases that exist. Then the creation of valuable evidence will be possible."

Besides the academic registries, Japanese public institutions such as MHLW, PMDA, and the Japan Agency for Medical Research and Development (AMED) run and manage disease registries. The MHLW and AMED have begun to link databases and registries and standardize and centralize information from local universities, medical institutions, and governmental agencies through the Clinical Innovation Network (CIN).[8] Plans for CIN beyond 2021 include using RWD sources other than registry data to develop innovative drugs and devices.

The MHLW began operating the NDB in 2009.[9] The NDB collects information on health insurance claims, specific health checkups, and health guidance, as stipulated in the "Act on Assurance of Medical Care for Elderly People."[5] Since records are collected through the National Health Insurance (NHI) system, the database provides information on 95% of people registered for healthcare in Japan. [9]

Access was restricted to researchers at the program's start but now allows access to third parties. A presentation in 2021 by AMED reports that the NDB is working toward consolidating and sharing data related to lifelong human health from infancy to death. The Long-term Nursing Care database (DB) and NDB were integrated to achieve that objective.[10]

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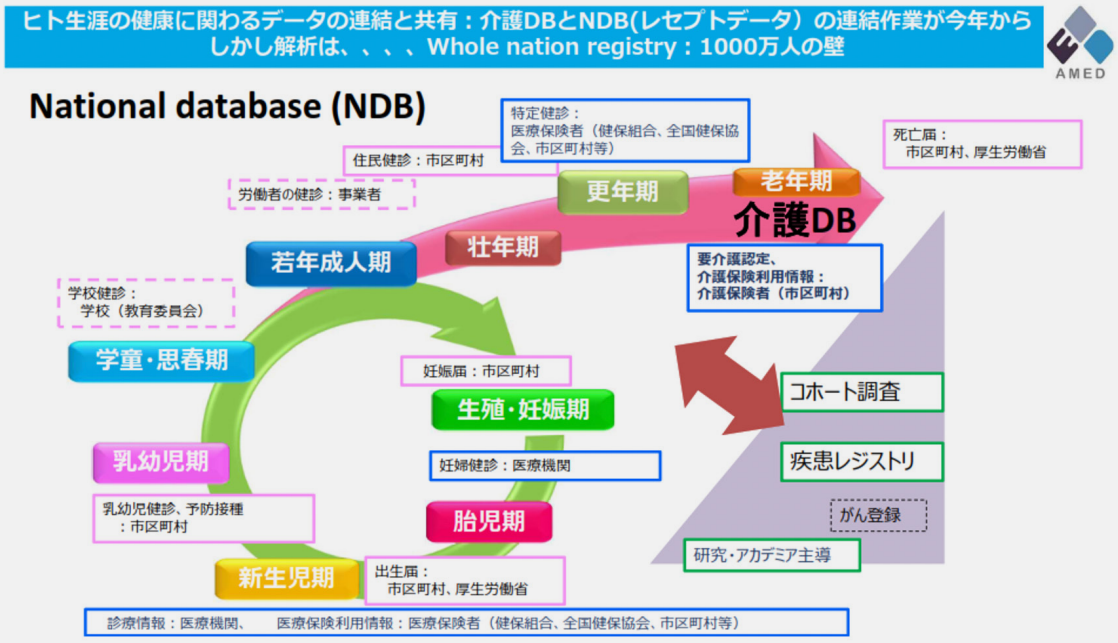

Figure 1. National Database Mission: to gather health care data from infancy to death of all people in Japan. Figure source: Japan Agency for Medical Development (AMED) Research Project for Harmonization and Evaluation of Pharmaceutical Regulations.[10]

Lack of motivation to conduct observational studies

Whether companies want to invest in studies that are not required by regulatory authorities might be the most important issue to solve. The NHI pricing system demotivates pharmaceutical companies, says Dr. Komiyama. Currently, pharma is not required to conduct scientific observational studies using RWD/RWE during pre-approval or eight-year post-marketing stages in the system.

"Even if you don't do anything scientific, the re-examination will be approved if drug usage data is diligently collected. So, for example, let's say we follow up on 3,000 patients who had used the drug and do surveillance. [All we need to do is] collect case reports from physicians, [and no analysis is required]."

Specifically, during the drug-re-examination period, analyses of the cause of an adverse event or effectiveness in specific patient groups are not required, according to Dr. Komiyama. These are carried out elsewhere in the US and Europe and might be required by those regulatory bodies.[11]

Therefore, the regulatory body in Japan approves the re-examination without these additional studies, and pharmaceutical companies can continue selling their drugs at the agreed, reduced price.

In addition, "anti-innovation is built into Japan NHI pricing system," says Dr. Katayama. "The price is automatically reduced during the patent period [according to the NHI pricing system], even if a drug has high value and is innovative. Thus, the Japanese pharmaceutical industry can be seen as an unattractive market and not worth the investment."

Dr. Komiyama, Dr. Katayama and others believe that this anti-innovative approach to pricing medicines in Japan further undermines the incentives for investing in studies involving RWE in Japan.

SECTION 4

The way forward

De-identify data to enable access and interoperability

The Act on Personal Information Protection, Law No. 119 (April 1, 2022)[12] and Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects Ethical Guideline (March 10, 2022)[13] protect patient data in all forms. However, these regulations do not allow private businesses to access and use the information unless patients consent. Therefore, pharmaceutical companies must comply with these regulations and obtain permission beforehand. An alternative method is to partner with academic institutions that can access the information for educational purposes.

But there is another solution to the problem.[5] In 2018, the Next Generation Healthcare Infrastructure Act (NHIA) was enacted to protect the identity of patients by allowing licensing companies to access, anonymize (de-identify), and store the personal medical data in a database for use in a study. In this case, the patients would not be required to provide informed consent to use their data.

In 2020, NTT DATA Corporation was the first to become a "Certified Business Operator Handling Medical Data," with others following. In addition, the Japan Medical Association Medical Information Management Organization became a "Certified Anonymizing Processor of Medical Data." However, there is no

governmental body to review the data quality of these individually de-identified databases for clinical study use. The NHIA also has the interoperability of healthcare records as its goal, though Japan does not have centralized, national data collection and storage rules across medical institutions yet.

Digitize personal health records to link databases

The Medical Affairs Committee and Communication Committee of PhRMA in Japan held a press seminar on RWD and RWE in Japan Revealed by the COVID-19 Pandemic: Current Status and Issues: How will Japan's healthcare change with the advance of digitalization?

PhRMA proposes to link medical records to the national identification number (My Number), educate the public on the usefulness of linking the data, and ensure the safe handling of personal information, says Dr. Katayama.

"Executives of pharmaceutical companies dream of being able to centrally manage registry data and the personal health record of the entire nation from birth to death, and to use it quickly to make various decisions based on the latest data in real-time."

To achieve this, Dr. Katayama explains, the committee proposes the digitization of RWD because it will enable clinicians to make evidence-based decisions, help tailor treatments to individuals, and accelerate development of drugs for patients with unmet needs.[14]

Ensure data quality and reliability of analysis methods

Essential to ensuring quality, as stated in the guidance, are "1) reliability of the data source, 2) transparency of the study design and analysis, and 3) reliability of the results to generate RWE." [4]

Dr. Sugitani says, "building a database that satisfies 1) reliability of the data source, is the most time-consuming step, requiring a long-term perspective. However, once step 1) is satisfied, steps 2) and 3) can be resolved with data science solutions."

Specifically, he explains that data scientists, mainly at the Food and Drug Administration (FDA), have developed a new Bayesian borrowing method that utilizes real-world registry data as a hybrid control.[15]

Researchers "borrow" data from previous studies using the Bayesian method, which would allow adding retrospective data to the control of studies with small patient numbers.

He believes, "The study design is easy to understand even for non-statisticians and will be very useful [because disease registry data can then be used] for regulatory applications."

However, Japan has not used this approach yet. According to Dr. Katayama, Japan seems to be lagging behind the rest of the world in applying new statistical methods, which would require an openness to advances in biomedical research.

As a physician educated in Japan, he says, "Medical education in Japan has not been fully exposed to the wave of globalization, and students are afflicted with Galapagos syndrome because they are only exposed to textbooks written by Japanese professors. Thus, Japanese drug development and safety monitoring have been influenced by those Japanese Key Opinion Leaders who believe Japanese are unique from the rest of the world."

He explains that because Japan is an island nation with almost a single ethnic group, the people might not have a global perspective. He believes that this attitude prevents objective and scientific evaluation of a drug's benefits and risks.

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SECTION 5

Vision for utilizing RWD/RWE in the Japanese pharmaceutical industry

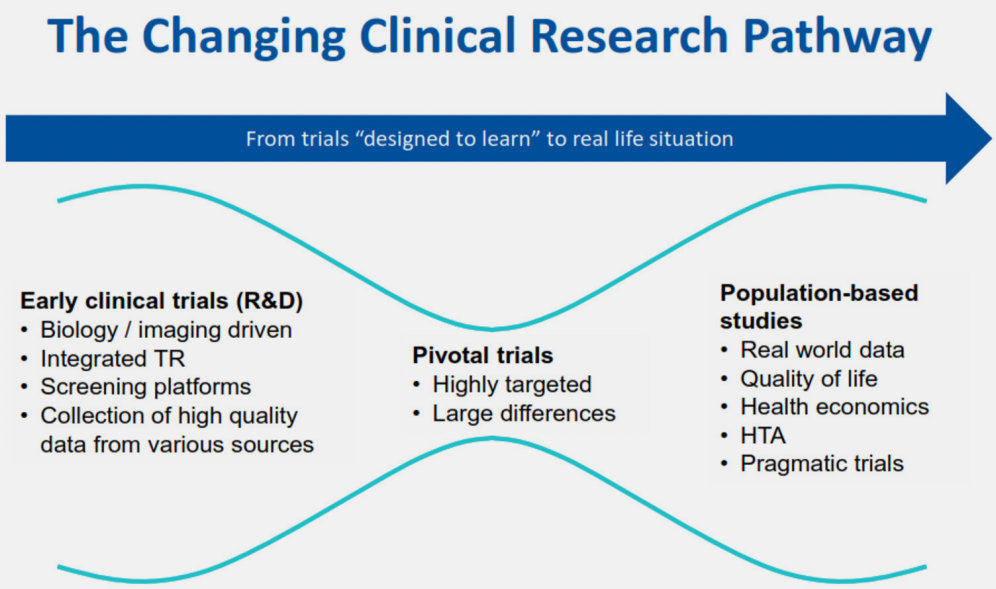

Figure 2. New developmental schemes based on the understanding of the disease lead to informed pivotal trial designs and opening up to real-life issues. Used with permission. Burock et al. Eur J. Cancer (2013)[16]

Take a hybrid approach for using RWD in registries and databases

Pharmaceutical companies do not typically develop a disease registry for proprietary use. Thus, Dr. Sugitani proposes a hybrid registry approach, "in which companies collaborate with existing registries owned by universities and academic societies to acquire additional information necessary for regulatory submissions as appropriate."

Tailor treatments according to a patient's background

Precision medicine is all the buzz these days. It is all about targeting the right patient groups and generating high-quality comparative effectiveness evidence. These can be done by linking the drug development process and healthcare models to provide affordable care, writes Denis Lacombe and colleagues of the European Organization for Research and Treatment of Cancer (EORTC), Brussels, Belgium.[2]

And Dr. Komiyama points to the importance of understanding the kinds of RWE studies (to the left and right in Figure 3) that might be conducted as currently showcased by the EORTC in Figure 2.

"Global development is becoming the norm," says Dr. Komiyama.

"It is important to consider factors such as patient and environmental factors in relation to benefits and risks of the drug given to individual patients, whether they are Japanese or non-Japanese. This leads to tailor-made medicine. Thus, by linking the wealth of patient data to drug development, we will be able to predict more than we do now, on the effectiveness and risks of the drug."

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