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Systems, Regulations and Utilization of Real-World Data Including Healthcare Database and Disease Registry in Drug Development and Post-Approval Evidence Generation in Japan

Makoto Nagaoka[1]*, Yuki Tajima[2] and Tomoko Kato[3]

[1]Global Regulatory Science and Policy, Global Regulatory Affairs, Sanofi KK, Japan
[2]Real World Evidence Generation Partnering, Medical Affairs, Sanofi KK, Japan
[3]Biostatistics and Programming, Clinical Science and Operations, Sanofi KK, Japan

Abstract

In Japan, the system and regulations regarding the utilization of the big data in healthcare or real-world data (RWD) for drug development are being established. A large-scale database of electronic medical information for post-marketing pharmacovigilance, the Medical Information Database Network (MID-NET®), and the Clinical Innovation Network (CIN) for utilizing disease registries have been created, and guidelines have been issued in sequence from those related to post-marketing database surveys. At present, the utilization of RWD in pharmacovigilance is still largely based on drug use results survey (a kind of product registry), but there are increasing cases of utilizing healthcare big data, such as medical information databases in hospitals and health insurance databases. It is expected that utilization of RWD in clinical development will become more active after the establishment of guidelines and the pilot run of the regulatory system in the future.

Keywords: Real-world data • Disease Registry • MID-NET® • Clinical Innovation Network • Personal information • Drug development • Post-marketing

Introduction

It has been a long time since the utilization of big data in the industrial world has become active. According to the 2012 White Paper on Information and Communication of the Ministry of Internal Affairs and Communications, Japan [1], a total of eight types of data are classified, including social media data, multimedia data, website data, customer data, sensor data, etc. Well-known examples of big data are traffic dynamics and purchasing information collected through Global Positioning System and mobile payment/digital wallet functions of smart phones, which are utilized to provide services that meet individual needs and improve the efficiency of business operations.

Advances in science have made drug development diversified, and the potential of various modalities as pharmaceuticals has been pursued, and drug development for diseases that have been difficult to treat so far has been attempted. Along with this situation, clinical trial design and data to be utilized are diversifying. Real World Data (RWD) can be raised as one of such data. Definition of RWD has not been prescribed in regulations in Japan. However, according to the definition of RWD by Food and Drug Administration (FDA), "Real-world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." As specific examples, Electronic Health Records (EHRs), Claims and Billing Activities, Product and Disease Registry, Patient-Generated Data Including in Home-Use Settings, Data gathered from other sources that can inform on health status, such as mobile devices and so on [2]. Hereafter, the definition of RWD in this paper follows the definition of FDA.

The use of big data in healthcare, especially as RWD in drug development and pharmacovigilance in Japan has been delayed compared to Europe and the United States, but it has become more active in recent years due to the development of regulations such as the formulation of various laws [3-5] and guidelines, and efforts have been initiated to utilize RWD in the field of drug development and pharmacovigilance accordingly. At the same time, through such efforts, various issues and problems in utilizing RWD in drug development and pharmacovigilance are becoming apparent.

Literature Review

In this paper, regarding the utilization of RWD in drug development and pharmacovigilance in Japan, we will give an overview of development of regulations, measures, policies, use cases and issues, and consider prospects. As healthcare databases, there are "National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB)" by the Ministry of Health, Labour and Welfare (MHLW), and the commercial medical information database by private companies, but in this paper, we focus on the Medical Information Database Network (MID-NET®) and Clinical Innovation Network (CIN), and outline the measures and policies for their construction and examples of their utilization in drug development and pharmacovigilance.

Medical Information Database Network (MID-NET®)

MID-NET® is one of the initiatives in MIHARI Project [6] led by Pharmaceuticals and Medical Devices Agency (PMDA). MIHARI Project aims to build a system for implementing drug safety measures through quantitative evaluation by means of pharmacoepidemiological methods by secondary use of electronic medical information. In MIHARI Project, system development began in 2009, and utilization for safety measures began in 2015. MIHARI Project uses medical data such as health insurance claim data, Diagnosis Procedure Combination (DPC) data and electronic medical records. In MIHARI

***Address for Correspondence:** Nagaoka M, Global Regulatory Science and Policy, Global Regulatory Affairs, Sanofi KK, Japan, E-mail: Makoto.Nagaoka@sanofi.com*

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Project, MID-NET® is a system for collecting and analyzing electronic medical records, DCP data and claim data of base medical institutions nationwide on a large scale (currently 10 institutions) and is operated by PMDA. According to PMDA, the significance and purpose of MID-NET® and the outline of its utilization are as follows [7].

- Since MID-NET® directly grasps and evaluates Adverse Drug Reactions (ADRs) using electronic medical information stored in a database, it is possible to evaluate the frequency of occurrence of ADRs that could not be grasped by the conventional ADR reporting system. In addition, since it is possible to collect ADRs and actual administration conditions that reflect the real world swiftly, at low cost, and actively, qualitative improvement and sophistication of drug safety measures, which have been conventionally carried out based on information reported from medical sites, will be promoted.
- MID-NET® extracts electronic medical information, such as electronic medical records and health insurance claim data accumulated in a database at each medical institution since 2009. PMDA preliminary examines the propriety of MID-NET® utilization by applicant. As a general rule, PMDA seeks the opinions of the board of experts consisting of independent third parties for the decision. Furthermore, the results obtained by utilizing MID-NET® should be disclosed in principle from the viewpoint of public interest. In order to prevent the possibility of identifying an individual, it is evaluated whether the result can be published based on the publication standard (the part where the total number of patients is small must be masked). In making that decision, PMDA seeks the opinions of the board of experts as necessary.
- The information on MID-NET® is anonymized, and since MID-NET® is operated based on Article 15 of the Pharmaceuticals and Medical Devices Agency Act (Act No. 192 of 2002). According to the provisions of the law, it is not necessary to obtain the informed consent from the person in advance for collecting, providing and utilizing the information by MID-NET®, but it is possible for the person to refuse usage of his/her medical information by applying to the base medical institution where the person treated.

MID-NET® has started accepting application of database utilization from April 1, 2018 and has been used 16 times so far [8]. Of these, 10 cases are usage by PMDA, one case is usage by a university, and the remaining five cases are usage by private companies. The use of private companies is mainly for post-marketing surveillance, and four out of five cases have such an objective.

Pfizer is conducting a post-marketing database survey using MID-NET® for the purpose of investigating safety concerns related to the reexamination application for Ibrance® Capsules (palbociclib), which was approved in September 2017. Myelosuppression (neutropenia) is selected as a safety concern, and feasibility is being examined prior to conducting the survey [8]. Daiichi-Sankyo is conducting a post-marketing database survey using MID-NET® for the purpose of investigating the safety concerns related to the reexamination application for Pralia® Subcutaneous Injection Syringe (denosumab), in which patients with rheumatoid arthritis are targeted, and the degree of risk of developing hypocalcemia in the group of patients who received the drug for the first time after July 2017 is evaluated in comparison with the group of patients who did not receive denosumab [8,9]. Similarly, for Minnebro® Tablets (esaxerenone), a post-marketing database survey using MID-NET® is being conducted to confirm the proper use of esaxerenone and the occurrence of hyperkalemia in patients prescribing esaxerenone [8]. In addition, MSD is using MID-NET® to investigate the safety concerns related to the application for reexamination of Atozet® Combination Tablets (ezetimibe atorvastatin calcium hydrate) [8].

Clinical Innovation Network (CIN)

MID-NET® is a system for collecting and analyzing electronic medical information on a large scale. On the other hand, CIN is a system promoted by MHLW and the Japan Agency for Medical Research and Development (AMED) for the purpose of creating an environment for utilizing disease registries in Japan. It was launched as one of the measures for medical innovation while the cost of drug development is increasing [9]. The goals and basic policies of CIN are as follows [10].

► **Goals**

- Based on regulatory science, Japan's competitiveness in the development of pharmaceuticals and medical devices will be reinforced by establishing an environment for developing innovative pharmaceuticals utilizing the disease registration system.
- With consideration for transparency and personal information, an organization/system for collecting and analyzing real-world data obtained in medical treatment will be established, and it is effectively utilized in drug discovery and medical settings.
- As a result, healthy life expectancy will be extended by promptly providing new drugs to the public.

► **Basic policies**

- In order to promote the establishment of an efficient clinical trial, post-marketing surveillance, and clinical research system utilizing the disease registration system, and to promote the development of pharmaceuticals and medical devices from Japan, the following measures will be taken.
  - ♦ In addition to organizing information on disease registration systems that are being developed in Japan, a system to solve problems to promote clinical trials, post-marketing surveillances, and clinical research will be established.
  - ♦ Based on regulatory science research, and in consideration of the trends of overseas regulatory authorities, an environment such as international cooperation to utilize the disease registration system for clinical trials and post-marketing surveillances will be established. Requirements for disease registration system (by application) and reliability standards will be established and thereby guidelines for the use of disease registration systems for new drug application and re-examination will be established.
  - ♦ Based on the verification results, a system for maintenance and management of disease registration at the expense of the beneficiary will be established.

The background to the establishment of CIN is the Healthcare Policy decided by the Cabinet in July 2014. In the Healthcare Policy, as a measure for research and development in the medical field that contributes to the provision of the world's highest level of medical care, it was stated that the environment for research and development in the medical field should be improved by the national government, and it was decided to drastically improve the environment for clinical research and clinical trials. Specifically, it was mentioned (1) to promote clinical research and clinical trials by comprehensively utilizing Translational Research Support Centers and Core Clinical Research Hospitals (hereinafter referred to as "Translational & Clinical Research Core Centers") and the National Research Centers for Advanced and Specialized Medical Care (hereinafter referred to as "National Center") which are being promoted in "Project of Translational and Clinical Research Core Centers" and by building Academic Research Organization (ARO) functions centered on them, (2) to establish a network (clinical innovation network) in which institutions such as national centers, etc. collaboratively centralize cases in order to promote clinical research and clinical trials, and (3) to build a mechanism to ensure that high-quality clinical research and clinical trials with international standards of quality are carried out by continuously making effective use of these resources while further improving their functions to achieve. In order to establish a research base, it was also regarded as an objective to share information such as a nationwide database of intractable diseases as wide as possible.

Under these circumstances, the establishment of CIN was proposed at the CIN Promotion Conference by MHLW in August 2015, and from

September 2015, the Working group of the National Center and the National Institutes of Biomedical Innovation, Health and Nutrition initiated discussion on the effective use of existing disease registries and the launch of new disease registries. Also, the Study Group supported by MHLW consisting of researchers from the National Center and academia considered problems that arise when using the disease registry in November 2015, January 2016, and March 2016. Furthermore, when establishing CIN, PMDA was required to give opinions based on its experience in examinations in order to build a registry that contributes to drug development and post-marketing safety measures, a CIN Working Group consisting of each group within PMDA was established in February 2016 [11]. The CIN Working Group considered (1) requirements for the registries in terms of clinical development and post-marketing surveillance, (2) methodology of the evaluation of the data in registries, and (3) how to secure reliability.

AMED supported the construction of a registry information integration base aimed at accelerating and promoting the CIN concept through the Project for Promoting Clinical Innovation Network, which was implemented from August 2017 to March 2020 [12]. As a result, a search system for domestic disease registries were built [13] and centralized aggregation of disease registry information were promoted. In addition, the introduction materials of each disease registry, the materials of the CIN research group by AMED, and "Registry Creation and Management Guide" which stipulates points-to-consider and the management body and the procedure from the start to the end of the construction of disease registry for those who build and operate the disease registry has been open to the public [14]. Furthermore, in the industry-academia-government joint registry utilization project of the Project for Promoting Clinical Innovation Network, (1) matching between institutions that have disease registries in areas where drug development should be further promoted (pediatric diseases, rare diseases, intractable diseases, etc.) and companies wishing to utilize them, (2) updates of disease registries according to corporate needs, and (3) supports to promote utilization of disease registry were implemented [15].

The project is currently conducting a fact-finding survey of domestic disease registries [16]. According to the interim results (N=557, as of July 12, 2018), neoplasms, psychiatric and behavioral disorders, musculoskeletal and connective tissue diseases based on the International Statistical Classification of Diseases and Related Health Problems (ICD)-10 classification account for more than half of the target diseases in the disease registries in Japan. Number of registered patients is less than 5,000 in about three-quarters of the registries and less than 500 in about half of them. In addition, many of them are aimed at collecting and analyzing clinical information, and the main purposes are utilization for medical treatment, natural history survey, grasp of the number of patients and patient distribution, and epidemiological research. On the other hand, as the current issues, the shortage of resources such as personnel and operating funds is the most prominent, followed by insufficient number of patient registration, insufficient utilization of registered data, and management of data quality.

Cooperation between CIN and MID-NET®

In the Basic Policy on Economic and Fiscal Management and Reform 2018 ~Realizing Sustainable Economic Growth by Overcoming the Decreasing Birth Rate and Aging Population~, which was decided by the Cabinet on June 15, 2018, the policy to link CIN and MID-NET® and whereby to utilize it for clinical research, drug development, safety measures, etc. was shown [17]. This is being considered as the Package for Promoting Clinical Evidence Construction. The aim is to improve the efficiency of clinical trials, clinical research and post-marketing safety measures (reduce the burden on medical staff) and improve the quality of each by expanding the MID-NET®-based system for collecting basic medical data accurately and automatically at nationwide level. It is expected, as a result, that the construction of clinical evidence from development to post-marketing safety measures will be further promoted, leading to improving the efficiency and cost reduction of drug discovery and post-marketing safety measures, and to contributing to the reduction of medical costs [18].

Table 1. Regulations related to utilization of RWD in Japan.

Date	Domestic Guidelines/Decisions	Major topics in Europe and the United States
31-Mar 2014	Guideline for Pharmaco-Epidemiological Study for Safety Assessment of a Pharmaceutical Using Medical Information Database	
Jun 2016	In Japan Revitalization Strategy, the decision to promote the construction of CIN and promote environmental improvement was made.	
Dec 2016		(US) 21st Century Cure Act
Jan 2017		(ICH) Reflection Paper on " GCP Renovation"
9-Jun 2017	Basic Principles on the Use of Medical Information Database in Post-marketing Pharmacovigilance	
Aug 2017		(US) Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
Nov 2017		(ICH) E8(R1) EWG
23-Jan 2018	Procedures for Developing Post-marketing Database Survey Plan	
23-Jan 2018	Guideline for Description of Protocols for Post-marketing Database Survey	
21-Feb 2018	Points to Consider for Ensuring Reliability in Post-marketing Database Surveys of Drugs	
1-Apr 2018	The revised GPSP ministerial ordinance was enforced. Post-marketing database survey was added as a type of post marketing survey.	
Nov 2018		(EU) Discussion paper: Use of patient disease registries for regulatory purposes considerations (public comment period: until Jun 2019, finalized at the end of 2019)
19-Dec 2018	Points to Consider for Ensuring Reliability in Post-marketing Database Surveys of Medical Devices	
Dec 2018		(US) Framework for FDA's Real-World Evidence Program (public comment period: until Apr 2019)
19-Jun 2019	Q&A on Points to Consider for Ensuring Reliability in Post-marketing Database Surveys of Drugs	
Nov 2019		(ICH) E6(R3) EWG
23-Mar 2020	Points to Consider for Ensuring Reliability in Post-marketing Database Surveys of Regenerative Medicine Products	
31-Jul 2020	Principles for Validation of Outcome Definitions Used in Post-marketing Database Surveys	

Establishment of regulations related to utilization of RWD in Japan

Guidelines that have been enforced: In Japan, since 2014, guidelines for the utilization of RWD have been developed (Table 1). We will refrain from explaining the contents of each guideline, but so far, around the time when the revision of the Good Post-marketing Study Practice (GPSP) Ministerial Ordinance on April 1, 2018 specified the post-marketing database survey, the development of guidelines for utilizing the medical information database in the post-marketing surveillance has been preceded. As a result, the guidelines related to reexamination/evaluation of drug use results, assurance of reliability, and principle of database utilization for post-marketing database survey have already been enforced. In this regard, at this time, if the regulatory use of RWD can be considered, it is a post-marketing database survey or a survey in conditional early approval system. Improvement of regulatory environment is underway to utilize RWD in new drug applications. As will be described later, discussions on guidelines for registry utilization are the main focus at this time, but it is expected that consideration will be given to the utilization of electronic medical records, health insurance claim data, etc. in the future. This series of actions is in line with trends in Europe and the United States.

Novel consultation systems for RWD in PMDA: In parallel with the development of the guidelines, PMDA consultation systems for RWD have been developed. In November 2017, the consultation system for epidemiological survey was established, whereafter novel PMDA consultation systems relating to disease registries for pharmaceuticals, medical devices and regenerative medicine products have been set up and operated on a trial basis since April 2019 (Table 2). As of the end of September 2020, the utilization status of these consultations is six for Registry Use Consultation (two pharmaceuticals, four medical devices), 1 for Consultation for Registry Compliance Inspection (one pharmaceutical), and as for Registry Use Planning Consultation, 17 consultations (11 pharmaceuticals, six medical devices) have been conducted, including consultations on the utilization of the registry in the existing consultation systems [19]. Regarding database surveys, Database Use Consultation for database operators have been in operation since April 2020, and Consultation for Database Compliance Inspection for pharmaceutical companies has been set up in late December 2020 (Table 2) [20].

Regulations for utilization of disease registry in new drug application: In May 2020, there were two draft guidelines presented to industry associations: "Basic concept regarding the use of the registry in new drug applications (draft)" and "Considerations on quality assurance of the utilization of the registry in new drug applications, etc. (draft)". In "Basic concept regarding the use of the registry in new drug applications (draft)", new drug application, reexamination/evaluation of drug use-results, etc. are assumed as cases of utilizing disease registry data. Presenting (1) feasibility check of a study in planning of clinical trials, (2) usage of registry data as an external control for evaluation of efficacy and/or safety, (3) usage of registry data for evaluation of efficacy and/or safety in the case that the registry contains data on drugs to be evaluated (e.g. supplemental new drug application) and (4) evaluation of safety and/or efficacy in post-marketing phase as cases of performing specific utilization, general considerations in common with these situations and special considerations for each situation are presented. In "Considerations on quality assurance of the utilization of the registry in new drug applications, etc. (draft)", there are two points summarized to consider in the registry used for dossier of new drug applications and in the applicants, who use the registry. Regarding the points-to-consider in the registry used for dossier of new drug application materials, in order to ensure the reliability of the registry itself, guidelines for the nine items that the applicant should pay attention to regarding management of the registry holder are the organizational system, ethical consideration and consideration in protection of personal information, computer system construction and management, data collection rules, handling of input data, quality control of computer systems and input data, creation of data sets for analysis, registry quality assurance, and the preservation of source records on registry owners and information are presented. In addition, as points-to-consider for applicants who use the registry, guidelines regarding contracts, data quality control by registry holder, statistical analysis, preparation of dossier for new drug application, and preservation of records by applicants are shown. In this draft guideline, it is suggested that regarding the considerations on reliability assurance when using registry data for re-examination or drug use-results evaluation, etc., existing guidelines such as points-to-consider regarding compliance in post-marketing database survey in pharmaceuticals, medical devices, and regenerative medicine products and the Q and A should be referred. The above two draft guidelines are expected to be finalized and issued after public comments to be implemented in near future.

Precedented cases of drug development using RWD for new drug application in Japan

Table 3 shows the cases that have obtained regulatory approval in Japan using RWD. At present, there are seven cases. Of these, methotrexate and methylprednisolone sodium succinate are based on the requests of academic societies related to the indication, and are categorized as public knowledge-based application based on the examination by "Handling of medical drugs for off-label use" and "The Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs", respectively, in which Japanese data in the registry and survey on the use of the academic society are used as public knowledge. The remaining five cases other than these two ones have

Table 2. Novel PMDA consultation systems for RWD.

Name	Target	Dept of PMDA	Content
Epidemiological Survey Consultation	Pharmaceutical companies	Each review department	For the purposes such as reexamination / reevaluation application for approved drugs or post-marketing surveillance for biosimilars, to give guidance and advice on the design of drug use results survey or post-marketing database survey.
Registry Use Consultation	Academia	Compliance	Regarding registries that may be used for new drug applications or reexamination applications, to advise the concept of a plan premised on the use of registries and general ideas for improving the quality and reliability of registries for the holders (limited to academia such as universities, research institutes, academic societies, etc.).
Registry Use Planning Consultation	Pharmaceutical companies	Each review department	In the new drug applications or reexamination applications, when you want to utilize the registry in evaluating the effectiveness and safety of a specific item, the validity of use and the sufficiency of the evaluation items in the usage plan of the registry according to the purpose of utilization etc. to consult. It doesn't matter if the registry has been built or you are planning to build the registry.
Consultation for Registry Compliance Inspection	Pharmaceutical companies	Compliance	For individual items scheduled for new drug applications or reexamination applications using the registry, to confirm and advise on compliance of the registry before application or post-marketing surveillance.
Database Use Consultation	Database operators	Compliance	For databases that may be used for new drug applications or reexamination applications (purposes of use (new drug application / reexamination application) and target disease areas are assumed), to give guidance and advice on the concept of planning based on the utilization of the database, and the general concept for improving the quality and ensuring reliability of the database.
Consultation for Database Compliance Inspection	Pharmaceutical companies	Compliance	For individual items scheduled for new drug application or reexamination using the medical information database, to advice on the concept of ensuring the reliability of the database before the start of the survey using the database, or to confirm the reliability of the survey before new drug application.

Table 3. Cases using RWD for new drug application in Japan.

Approval year	Generic name (Brand name)	Application criteria	Efficacy or effect	RWD and endpoints
Apr 2007	Alglucosidase alpha (Myozyme® intravenous infusion)	New active ingredients	Glycogen storage disease type II	•External control group / overseas medical records: comparison with retrospective medical history study (US) •Invasive ventilator free survival rate at 18 months of age
May 2011	Algatroban hydrate (Novastan® HI inj. / Slonnon® HI inj.)	New indication	Heparin-induced thrombocytopenia type II	•External control group / overseas medical records: retrospective collection of cases that met the selection criteria and did not use antithrombin drugs at the study site •Death from all causes, amputation of limbs and development of new thromboembolism within 37 days
Feb 2011	Methotrexate (Rheumatrex® capsules)*	New indication and doses	Rheumatoid arthritis	•Public knowledge-based application by using the disease registry (REAL) (Japanese)
Jun 2013	Tacrolimus hydrate (Prograf® capsules)	New indication	Polymyositis / dermatomyositis	•External control group / literature (Japanese): retrospective collection of data on initial treatment with steroids alone was insufficient, resulting in a comparison with the published literature. •Survival rate
Mar 2013	Methylprednisolone sodium succinate (Solu-Medrol® for intravenous use)*	New indication and doses	Acute aggravation of multiple sclerosis	•Public knowledge-based application by using the survey on the use (Japanese) conducted by the Japanese Society of Neurology
Aug 2015	Asfotase alpha (Strensiq® for subcutaneous injection)	New active ingredients	Hypophosphatasia	•External Control Group/Overseas electronic medical records: comparison with a natural history study (US) •Survival rate and invasive ventilator free survival rate
Mar 2020	Viltolarsen (Viltepso® inj.)	New active ingredients	Duchenne muscular dystrophy	•Natural history study conducted by Cooperative International Neuromuscular Research Group •Motor function

*Public knowledge-based application based on the examination by "Handling of medical drugs for off-label use" (methotrexate) or "The Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs" (methylprednisolone sodium succinate).

undergone the normal approval application process, and the common feature is that they have been designated as orphan drugs. In addition, out of the five ones, four cases except for tacrolimus hydrate use the disease registry as an external control, but each case uses overseas data. At present, there is no example of using the data of the domestic disease registry as an external control for new drug application in Japan. It is suggested as background for this situation that the disease registry in which collected data can be used for new drug applications has not been sufficiently developed in Japan, that there was no system (guidelines, PMDA consultation, etc.) for utilizing the disease registry for new drug applications and that companies resultantly had to be reluctant to submit new drug application by using the disease registry. In the future, it is expected that various systems such as the above-mentioned guidelines and PMDA consultation will be established, and clinical development and new drug applications utilizing the disease registry will be activated by social understanding and recognition of the importance and significance of the disease registry.

Precedented cases of post-approval evidence generation by RWD

Utilization of RWD including disease registries in clinical development and new drug application has not yet progressed in earnest in Japan, and the environment for implementation including guidelines is being prepared. On the other hand, the utilization of RWD such as healthcare database in post-marketing surveillance of pharmaceutical products has been progressing. As mentioned above, the background factors are that each guideline has been established and that the official operation of MID-NET® has started. In addition to the utilization of MID-NET®, post-marketing surveillance of pharmaceutical products utilizing the disease registry has begun to be conducted. The following are three cases. The first two are Temcell® HS Inj. (human (allogeneic) bone marrow-derived mesenchymal stem cells) and Kymriah® (Tisagenlecleucel) and categorized as a regenerative medicine product. The third one is Viltepso® Injection (Viltolarsen), which was also mentioned in the previous section. In these three products, all-case survey is being conducted as post-marketing surveillance. Temcell® HS Inj. is the first regenerative medicine product to receive regulatory approval in Japan and was approved in September 2015 for the indication of "acute graft-versus-host disease after hematopoietic stem cell transplantation." As a condition of approval, it is required to carry out a drug use-results survey of all cases using Temcell® HS Inj. during the re-examination period. In collecting data from this drug use-results survey, "Transplant Registry Unified Management Program (TRUMP)" has been used which is based on the hematopoietic cell transplant registry operated by The Japanese Data Center for Hematopoietic Cell Transplantation and The Japan Society for Hematopoietic Cell Transplantation [21]. This registry is harmonized with the survey items of Western registries (Europe: The European Society for Blood and Marrow Transplantation, US: Center for International Blood and Marrow Transplant Research), and data can be used interchangeably. It is also part of the patient registration system for regenerative medicine product that MHLW and PMDA started operating in 2017 [22].

Kymriah® is a Chimeric Antigen Receptor T-cell (CAR-T) therapy, which was approved in Japan in March 2019 for a relapsed or refractory CD-19-positive B-cell acute lymphoblastic leukemia and relapsed or refractory CD-19-positive diffuse large B-cell lymphoma. As a condition of approval, it is obliged to conduct a survey on the results of use in all cases in post-marketing until data on a certain number of cases are collected. In response to this, a system has been established to carry out long-term follow-up for all administration cases as a post-marketing database survey, and the basis is the hematopoietic cell transplant registry as in the case of Temcell® HS Inj. The hematopoietic cell transplant registry has TRUMP, which collects and manages basic items for hematopoietic cell transplantation as described above, and additionally has established a data collection and management system for CAR-T cell therapy to support this post-marketing surveillance.

Viltepso® Injection is an oligonucleotide therapeutic agent with exon-skipping effect that was approved in Japan in March 2020 and is a therapeutic drug for Duchenne muscular dystrophy (DMD) patients with a gene mutation that responds to exon 53 skipping of the dystrophin gene. This drug was jointly developed by the National Center of Neurology and Psychiatry (NCNP) and Nippon Shinyaku. The First in Human trial was conducted as an investigator-initiated clinical trial by NCNP in DMD patients [23], in which efficient patient recruitment was successfully achieved by using a national registry for neuromuscular diseases constructed by NCNP (Remudy: Registry of Muscular Dystrophy) [24]. Viltepso® Injection received SAKIGAKE designation for DMD as a planned indication in October 2015 and also received orphan drug designation for "Duchenne muscular dystrophy, which has been confirmed to have a deletion of the dystrophin gene treatable by exon 53 skipping" in August 2019. In addition, upon its regulatory approval, the conditional early approval system is applied. Based on this background, in addition to formulating and implementing a risk management plan, (1) execution of a drug use-results survey for all cases during the re-examination period, and (2) execution of a clinical trial (Phase III trial) and a survey using a domestic registry to confirm

efficacy and safety are required as approval conditions. Remudy is planned to be used in conducting the survey.

In the above cases, existing disease registries owned by academia are utilized, additionally building a data collection and management system as needed for post-marketing surveillance. Under this system, the data collected through the disease registry is stored on the academia side, which is the registry owner, so the marketing authorization holder who conducts post-marketing surveillance receives the data secondarily and utilizes them for post-marketing surveillance.

Current challenges and promising solutions

It can be mentioned that what is important in promoting the utilization of RWD is the validity of data according to fit-for-purpose, the validity and reliability in utilization purpose, the handling of personal information and the organizational and operational system for data collection and maintenance. The study protocol that clarifies the outcome and populations to be examined and the type and quality of data source are the basis for considering the validity of data according to fit-for-purpose. Data sources include claim data/electronic medical records and disease registries. In this paper, we have outlined MID-NET® as the basis for electronic medical records and claim data and CIN as the basis for disease registries. Generally, in use of the claim data, to confirm the validity of the outcome definition is important in terms of the difference between the disease name used for claim and the actual diagnosis. The electronic medical record data may include test results and image data specialized for a therapeutic area, which are not always structured data. There is also a problem that compatibility is not guaranteed between multiple electronic medical record systems in operation and data integration is not easy. Regarding the disease registry, the consistency of the collected data items within the registry is guaranteed to some extent, but whether the content is appropriate for drug development depends on the purpose of establishing and operating the disease registry. In Japan, MID-NET® based on electronic medical records and claim data and CIN based on disease registries have been established and operated as national-level efforts from the perspective of data sources. Since the infrastructure development in terms of hardware is steadily progressing, it can be considered that various problems related to data sources have been dealt with to some extent. For example, Standardized Structured Medical Information exchange (SS-MIX) by MHLW is used in MID-NET® to address the issue of ensuring compatibility between electronic medical record systems.

In addition, certain rules including legislation have been created for addressing the challenges such as the validity and reliability in utilization purpose and the protection of personal information and the secondary use of data. What is important about the validity and reliability in utilization purpose is how to specify the handling of RWD in the guideline and how to operate the guideline. As for post-marketing database survey, several guidelines have been released and operated such as “Basic Principles on the Use of Medical Information Database in Post-marketing Pharmacovigilance” and “Points to Consider for Ensuring Reliability in Post-marketing Database Survey of Drugs”. On the other hand, as for the handling of RWD in the “new drug application”, as mentioned in the section on “Establishment of regulations related to utilization of RWD in Japan”, “Basic concept regarding the use of the registry in new drug applications (draft)” and “Considerations on quality assurance of the utilization of the registry in new drug applications, etc. (draft)” are currently being developed. Both draft guidelines are slightly conservative at this moment and are by no means enough to facilitate the flexible use of disease registry data for new drug application. In the future, it is expected that it will be finalized after further discussions between regulators, academia and industry, but in addition to utilization for the sole purpose of obtaining definitive conclusions, utilization for obtaining preliminary information and reliability assurance in such utilization should be considered in the guidelines. In addition, even in the subsequent operation, it should always be appropriate and flexible with “Fit for purpose” in mind, and such an attitude is desirable from the viewpoint of promoting the utilization of disease registry data, and as a result, it is thought that the utilization of disease registries and RWD for new drug application will become mature.

“Act on the Protection of Personal Information” and “Act on Anonymized Medical Data That Are Meant to Contribute to Research and Development in the Medical Field” are the basis for responding to issues related to the protection of personal information and the secondary use of data [3-5]. Act on the Protection of Personal Information came into effect in April 2005 and is to be reviewed every three years. Under Act on the Protection of Personal Information, when providing sensitive personal information such as medical history to a third party, opt-in (consent provided by the person in advance) instead of opt-out (stop providing at the request of the person) is needed except for academic research. In addition, anonymously processed information obtained by processing personal information so that a specific individual cannot be identified and making it impossible to restore the personal information can be provided to a third party without the consent of the person. For this reason, individual medical institutions can perform the anonymous processing of their medical information (personal information) by themselves or outsourcing and provide it to users without their consent. Under Act on the Protection of Personal Information, there are problems such as (1) there are opt-in requirements, and (2) in anonymous processing, medical institutions remain responsible for anonymous processing, anonymous processing is required for each individual medical institution, and it is difficult to judge outsourcing vendors’ capability of anonymous processing (when anonymous processing is outsourced). Act on Anonymized Medical Data That Are Meant to Contribute to Research and Development in the Medical Field was enforced in May 2018 due to the aforementioned problems. Act on Anonymized Medical Data That Are Meant to Contribute to Research and Development in the Medical Field stipulates opt-in and opt-out that meet certain requirements regarding the provision of sensitive personal information, and the introduction of a system of certified vendors regarding anonymous processing. As a result, it has become possible that medical institutions provide certified vendors with medical information such as sensitive personal information, and that certified vendors provide users with anonymously processed medical information. Regulations on the handling of personal information are indispensable for promoting the utilization of RWD. Therefore, the aforementioned legislation is of great significance. However, it is suggested that further rules need to be created for information that can be personally identified by itself, such as genomic data and information that may be modified in anonymous processing, such as image data.

To the contrary, there is an urgent need to take measures to improve the organization and operation system in the future. Regarding the organization and operation system for data collection and maintenance, aside from commercial databases, it becomes a problem in MID-NET® and various disease registries operated by academia. PMDA initially estimated 18 items in the post-marketing surveillance as the number of MID-NET® utilization cases since 2021 [25]. However, the actual results are far below, and it will be difficult to maintain and operate MID-NET® as it is. One of the reasons is that the scale of patient data is small (5.05 million as of the end of December 2019), and the handling of analytical datasets is limited to on-site centers. These points need urgent improvement. On the other hand, regarding disease registries, it can be said that domestic disease registries are mainly constructed and operated in the areas of cancer and rare diseases from the contents shown in the CIN section. In these areas, it is often difficult to carry out randomized controlled trials due to the severity and rarity of the disease, so from the viewpoint of drug development, there is a high need for utilization of the disease registry as an external control group. However, it cannot be said that the utilization of disease registries in drug development is sufficiently advanced, and it is considered that there are issues regarding the operating organization/system /resources and the purpose/form of disease registry construction as the background. In the future, it will be necessary to first create a mechanism to ensure the maintenance and continuation of the disease registry. Unless such an environment is improved, promotion of utilization in drug development cannot be expected. Furthermore, quality control and scale of data will be important, and as an action for that, it will be necessary to deepen the understanding of patients and their families about the significance of the disease registry, and as a result, increase the number of registered patients. At the same time, it will be necessary to formulate and operate highly flexible guidelines based on scientific evidence that will lead to the promotion of utilization.

Conclusion

This is an overview of development of regulations, measures, policies, use cases and issues regarding the utilization of RWD in drug development and pharmacovigilance in Japan. The use of RWD in drug development and pharmacovigilance in Japan is not sufficient compared to the situation in Europe and the United States [26], but the environment is steadily improving. In the future, of importance are (1) reliability assurance and improvement of RWD acquisition method based on RWD generation process and "Fit for purpose", (2) improvement of environment for utilization of medical information database such as electronic medical records for new drug application, (3) promotion of the social understanding of utilization of RWD in drug development and pharmacovigilance.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article. There was no informed decision by anyone to sponsor this work, and there was no dedicated funding granted to carry out the research. The study was conceived of, executed on, and written up in the course of the authors' daily jobs.

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