

# Evolving Acceptance and Use of RWE for Regulatory Decision Making on the Benefit/Risk Assessment of a Drug in Japan

Kinue Nishioka<sup>1</sup>, Tomomi Makimura<sup>2</sup>, Akihiro Ishiguro<sup>3</sup>, Takahiro Nonaka<sup>4</sup>, Mitsune Yamaguchi<sup>5</sup> and Yoshiaki Uyama<sup>4,\*</sup>

There is growing interest in the utilization of real-world data (RWD) and real-world evidence (RWE) for regulatory purposes. However, there are challenges in the practical utilization of RWD to provide RWE as a basis for regulatory decision making. This article presents the regulatory initiatives in Japan and efforts taken to promote the utilization of RWD/RWE for regulatory decision making at the pre- and postapproval stages of a drug. There has been a rapid increase in the number of RWD cases evaluated for drug safety assessment in Japan. Nevertheless, more regulatory experiences and considerations are necessary for the utilization of RWD in the efficacy evaluation of a drug. Based on past experiences, data reliability and appropriateness of the methodology for analysis are the major discussion points in utilizing RWD and RWE for regulatory decision making. International harmonization of regulatory requirements is another important area in utilizing RWD and sharing the RWE globally. We describe our perspective on providing RWE, which is useful for regulatory decision making throughout a drug's life cycle.

Real-world data (RWD) and real-world evidence (RWE) have been actively discussed in terms of utilization for regulatory decision making on the benefit/risk assessment of a drug.<sup>1,2</sup> The US Food and Drug Administration (FDA) has initiated the Real-World Evidence Program<sup>3</sup> to evaluate the potential use of RWE in the regulatory setting. Final or draft regulatory guidelines related to RWD/RWE, such as the use of RWD/RWE for regulatory submissions, and general principles for conducting studies using the data from electronic health records or patient registries have also been published by many different regulatory agencies, including the FDA and the European Medicine Agency (EMA).<sup>4-7</sup>

Similar to the FDA and the EMA, we considered RWD as data obtained in actual medical environment and it includes medical records, claims, data from disease registries, product registries of drugs, medical devices, or regenerative medical products, and the other healthcare data sources, such as home appliances and mobile devices. In Japan, the Ministry of Health, Labour, and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have worked to promote the utilization of RWD/RWE throughout a drug's life cycle. In this paper, we summarize the regulatory initiatives in Japan for utilizing the RWD/RWE in the benefit/risk assessment of a drug and describe our perspective on the future challenges in utilizing RWD/RWE for regulatory decision making.

## JAPANESE REGULATORY GUIDELINES FOR PROMOTING UTILIZATION OF RWD/RWE IN A DRUG'S LIFE CYCLE

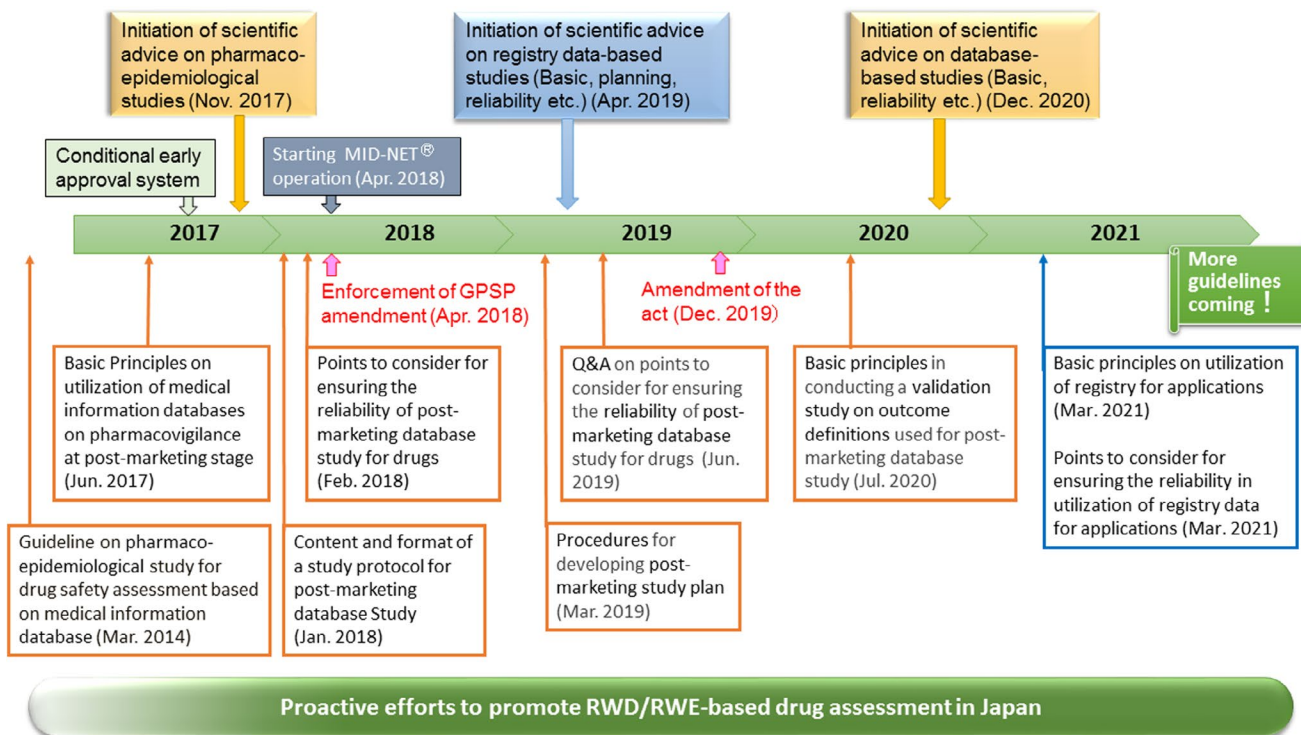
**Figure 1** summarizes the history of Japan's regulatory initiatives related to the RWD/RWE. Since 2014, many regulatory measures

have been implemented to promote the utilization of RWD and RWE in regulatory setting. For example, in 2017, a new scientific advice program on pharmaco-epidemiological studies was initiated for discussions with a marketing authorization holder about the design and plan for postmarketing studies, including a study utilizing RWD. In more recent years (2019 and 2020), new scientific advice programs targeting the registry data and database-based studies not only for pharmacovigilance but also for new drug applications were initiated. These scientific advice programs will offer opportunities for mutual understanding and problem solving between the PMDA and stakeholders, including pharmaceutical industries, investigators, or registry holders, regarding studies for generating appropriate RWD and RWE.

In parallel, in the last several years, related legislation and regulatory guidelines were amended or published by the PMDA or MHLW to promote the utilization of RWD/RWE throughout a drug's life cycle (**Figure 1, Table 1**).<sup>8</sup> For example, in 2014, the PMDA published a guideline on pharmaco-epidemiological studies for drug safety assessment based on a medical information database (see #1 in **Table 1**, same hereinafter). This guideline was the first document in Japan about the utilization of RWD by pharmaceutical industries. It describes points to consider how pharmaco-epidemiological studies are planned and designed for clinical safety assessment of a drug with the secondary use of medical information database. In 2017, the MHLW published the "Basic principles on utilization of medical information database on pharmacovigilance at post-marketing stage" (see #2 in **Table 1**). This was in response to the increased

<sup>1</sup>Office of New Drug III, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; <sup>2</sup>Office of Standards and Compliance for Medical Devices, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; <sup>3</sup>Office of Research Promotion, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; <sup>4</sup>Office of Medical Informatics and Epidemiology, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; <sup>5</sup>Office of Non-clinical and Clinical Compliance, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan. \*Correspondence: Yoshiaki Uyama ([uyama-yoshiaki@pmda.go.jp](mailto:uyama-yoshiaki@pmda.go.jp))

Received March 1, 2021; accepted August 25, 2021. doi:10.1002/cpt.2410



**Figure 1** History of Regulatory Initiatives in Japan for the utilization of RWD/RWE in the benefit/risk assessment of a drug. GPSP, Good Post-marketing Study Practice; RWD, real-world data; RWE, real-world evidence; Q&A, question and answer.

situations for utilizing the medical information databases for drug safety assessment as postmarketing surveillance, including the official launch of the operation of the MID-NET® by the PMDA in April 2018. At the same time, the ministerial ordinance on “Good Post-marketing Study Practice,” which sets the reliability standards for postmarketing studies conducted by a marketing authorization holder after approval of a drug was amended (see #4 in **Table 1**) to further improve the post-marketing pharmacovigilance in Japan. With this revision, a postmarketing database study was clearly defined, and relevant regulatory guidelines for these types of studies have also been published in the last few years, including the content and format of a study protocol (see #5 in **Table 1**), data reliability and quality assurance (see #6 and #8 in **Table 1**), validation study for definition of the outcome (see #10 in **Table 1**), and the best practice to develop an appropriate risk management plan of a drug for the investigation of a target concern based on the research question (see #7 in **Table 1**). In December 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 sold by marketing authorization holders, and collect information (including RWD) to ensure the appropriate use of pharmaceuticals and other medical products (see #9 in **Table 1**).

Furthermore, the revised “Japan Revitalization Strategy” in 2015 adopted by the Cabinet (Cabinet decision on June 30,

2015) promoted the use of novel clinical development methodologies, more specifically by creating the clinical innovation network project to establish an infrastructure for clinical development based on the disease registry information.<sup>9</sup> Since then, the PMDA has worked to promote the clinical innovation network project in collaboration with academia, the MHLW, and the Japan Agency for Medical Research and Development for the further utilization of registries in drug development. With reference to the latest situations about the utilization of the registry in drug development, in case traditional randomized clinical trials are not feasible, such as for orphan drugs, two guidelines titled “Basic principles on utilization of registry for applications”<sup>10</sup> and “Points to consider for ensuring the reliability in utilization of registry data for applications”<sup>11</sup> were published in 2021 (see #12 and #13 in **Table 1**). The utilization of RWD to evaluate the safety or efficacy of a drug for regulatory submission has also been encouraged when a drug was approved under the conditional early approval system implemented in 2017 (see #3 in **Table 1**). This was formally converted into the Act on Securing Quality, Efficacy, and Safety of Products, including Pharmaceuticals and Medical Devices in 2020 (see #11 in **Table 1**).

**EXAMPLES OF RWD/RWE USED FOR REGULATORY DECISION MAKING IN JAPAN**

**Cases at the pre-approval stage**

In Japan, some new drugs have been approved based on the evaluation of RWD as major evidence for the efficacy of a drug. Such examples are listed in **Table 2**. All three cases were designated as orphan drugs under the Act on Securing Quality, Efficacy,

**Table 1 List of regulatory initiatives in terms of amendment of legislation and guidelines relating to the utilization of RWD/RWE in pharmaceutical regulations in Japan (<https://www.pmda.go.jp/english/rs-sb-std/rs/0023.html>)**

#	Date	Issuing authority, Notification No.	Title
1	Mar 31, 2014	PMDA, Reference document	Guideline on pharmacoepidemiological study for drug safety assessment based on medical information database
2	Jun 9, 2017	MHLW, PSEHB/PED Notification No. 0609-8, PSEHB/SD Notification No. 0609-4	Basic principles on utilization of medical information databases on pharmacovigilance at postmarketing stage
3	Oct 20, 2017	MHLW, PSEHB/PED Notification No. 1020-1	Conditional early approval system for drugs
4	Oct 26, 2017 (Enforcement in April 2018)	Ordinance of MHLW No. 116	Amendment of ministerial ordinance on GPSP
5	Jan 23, 2018	PMDA, Reference document	Content and format of a study protocol for postmarketing database study
6	Feb 21, 2018	MHLW, PSEHB/PED Notification No. 0221-1	Points to consider for ensuring the reliability of postmarketing database study for drugs (medical devices/ regenerative medical products)
7	Mar 14, 2019	MHLW, PSEHB/PED Notification No. 0314-4, PSEHB/PSD Notification No. 0314-4	Procedures for developing postmarketing study plan (originally published by the PMDA in January 2018)
8	Jun 19, 2019	MHLW, Administrative Notice	Q&A on points to consider for ensuring the reliability of postmarketing database study for drugs
9	Dec 4, 2019	Act No. 145 of 1960 (Amendment Act No. 63 of 2019)	Amendment of the act on securing quality, efficacy and safety of products including pharmaceuticals and medical devices
10	Jul 31, 2020	PMDA, CRS Notification No. 0731002, CPE Notification No. 0731002	Basic principles in conducting a validation study on outcome definitions used for postmarketing database study
11	Aug 31, 2020	MHLW, PSEHB/PED Notification No. 0831-2	Conditional early approval system for drugs <sup>a</sup>
12	Mar 23, 2021	MHLW, PSEHB/PED Notification No. 0323-1, PSEHB/MDED Notification No. 0323-1	Basic principles on utilization of registry for applications
13	Mar 23, 2021	MHLW, PSEHB/PED Notification No. 0323-2, PSEHB/MDED Notification No. 0323-2	Points to consider for ensuring the reliability in utilization of registry data for applications

CPE, Center for Product Evaluation; CRS, Center for Regulatory Science; GPSP, Good Post-marketing Study Practice; MDED, Medical Device Evaluation Division; MHLW, Ministry of Health, Labour, and Welfare; PED, Pharmaceutical Evaluation Division; PMDA, Pharmaceuticals and Medical Devices Agency; PSD, Pharmaceutical Safety Division; PSEHB, Pharmaceutical Safety and Environmental Health Bureau; Q&A, question and answer; RWD, real-world data; RWE, real-world evidence.

<sup>a</sup> With the amendment of the Act on Securing Quality, Efficacy, and Safety of Products, including pharmaceuticals and medical devices in December 2019 (see #9), the conditional early approval system for drugs, which was originally introduced in 2017 (see #3), was formally enforced in 2020.

and Safety of Products, including Pharmaceuticals and Medical Devices. The orphan drug is designated in situations wherein the total number of patients with the specific disease condition in Japan is < 50,000.<sup>12,13</sup> Alglucosidase-alfa is a new active ingredient approved for the treatment of glycogen storage disease type II (GSD II).<sup>14</sup> In the review for approval, because the number of patients with the disease in Japan was very limited and the drug was already approved overseas, the benefit/risk of alglucosidase-alfa was evaluated on the basis of safety data from a few patients administered this drug in Japan and the efficacy/safety data of foreign clinical trials with an external control of the natural history data from the independent observational study. An objective end point (total survival rate and survival rate without support by invasive ventilation) was used to compare the results between the observational study and the clinical trial. An appropriate patient population as the external control group was selected from the observational studies to match the patient backgrounds with those of the clinical trial population based on the inclusion and exclusion criteria of the clinical trial. For the regulatory decision making, the severity of the disease (infantile-onset GSD II develops

symptoms and signs within the first 12 months of life, and most patients result in death within the first year of life due to cardiac or respiratory failure), the lack of existing therapies, and infeasibility of conducting randomized-clinical trials in Japan, as well as the methods for efficacy comparison were considered. This led to the conclusion that the efficacy evaluation of this drug utilizing RWD as an external control was useful and acceptable for approval.

In another case, argatroban hydrate was originally approved for the prevention of thrombosis in heparin-induced thrombocytopenia type 2 (HIT2).<sup>15</sup> The results of clinical trials submitted for this indication were reused in the subsequent application to extend the use of the drug for two additional indications: preventing coagulation of the perfused blood during extracorporeal circulation in patients with HIT2 (dialysis-HIT), and preventing coagulation during percutaneous coronary intervention (PCI) in patients with HIT2 (PCI-in-HIT).

The noninterventive data of patients as historical control (nonuse of antithrombin agents) were gathered retrospectively from sites that participated in the clinical trials. Those data were used to compare with data from the clinical trials. The efficacy of

**Table 2 Typical examples of a drug approved utilizing RWD as the major evidence for efficacy evaluation in the regulatory review**

Nonproprietary name	Indication	RWD utilized as major evidence in the regulatory review	Approval year/month	Category of application	Note
Alglucosidase-Alfa (Genetical Recombination)	Glycogen storage disease type II	Retrospectively collected natural history data	2007.4	A new active ingredient	Orphan drug
Argatroban hydrate	HIT type 2	Retrospectively collected data of cases at clinical trial sites	2011.5	A new indication	Orphan drug
Asfotase-Alfa (Genetical Recombination)	Hypophosphatasia	Retrospectively collected natural history data	2015.8	A new active ingredient	Orphan drug

HIT, heparin-induced thrombocytopenia; RWD, real-world data.

argatroban hydrate in dialysis-related HIT and PCI-in-HIT was similar to that for the existing indication based on the appropriate end point, that was residual blood in the circuit of extracorporeal circulation and activated clotting time values (e.g., satisfactory PCI results and development of major acute complications), respectively. In addition to the limited number of patients with the target disease in Japan, because argatroban hydrate has already been approved for the prevention of HIT2 and is the only drug that has been used in clinical practice in Japan, a retrospective evaluation of cases from the existing clinical trials based on RWD was useful and acceptable for approval.

Asfotase alfa is a new active ingredient approved for the treatment of hypophosphatasia.<sup>16</sup> In the review for approval, the efficacy of asfotase -alfa was evaluated based on the results of a multiregional clinical trial, including Japan and another foreign clinical trial with data of the natural history of the disease retrieved from an independent observational study used as an external control. Similar to the case of alglucosidase-alfa, a comparison of the results between the observational study and the clinical trials was based on an objective end point (mainly survival rate) in the appropriate patient populations (infantile-onset type hypophosphatasia) of clinical trials, considering the inclusion criteria of the observational study. An improvement by this drug in the survival rate compared with that in the external control group (natural history) was suggested. Considering the severity of the target disease (the mortality rate in critically ill pediatric patients is 50–100%), lack of existing therapies and the objective end points (survival rate), RWD-based efficacy evaluation of this drug was useful and acceptable for approval.

In addition to the cases described above, tacrolimus hydrate approved for the treatment of interstitial pneumonia associated with polymyositis and dermatomyositis. In this case, RWD as a historical control, such as the survival rate and progression-free survival rate in patients who were initially treated with a steroid monotherapy, were submitted for comparing with those in the single-arm, investigator-initiated clinical trial enrolling patients who were initially treated with tacrolimus hydrate and steroid in combination.<sup>17</sup> However, due to the widespread off-label combination use of steroids with immunosuppressive drugs in clinical practice, the actual number of patients collected for the historical control were very limited ( $n = 5$ ) and could not reach the target number. Therefore, these RWD were not used as the major evidence for regulatory decision making. Furthermore, as a recent case, viltolarsen, which was a new active ingredient designated as the “SAKIGAKE” drug, as well as subject to conditional early approval, was approved in March 2020 for the treatment of Duchenne muscular dystrophy, a condition caused by a deletion in the dystrophin gene, amenable to exon 53 skipping therapy.<sup>18</sup> A certain level of efficacy required for approval of the SAKIGAKE designation drug was achieved in the clinical trial; however, due to the limited number of Japanese patients in the clinical trials, the PMDA decided that more data collection after approval was indispensable. Therefore, it was planned to confirm the efficacy and safety of viltolarsen using a multiregional confirmatory clinical study and the registry called as “Remudy” (a Japanese disease registry for patients with muscular dystrophy).<sup>19</sup> As in this example, more extensive utilization of the registry data is expected to promote drug development not only as

an external control of clinical trials but also for the collection of efficacy and safety data of a drug at pre- and postapproval stages.

### Cases at postapproval stage

Drug safety assessment at postmarketing has seen the most advanced utilization of RWD/RWE in Japan. In a fiscal year 2009, the PMDA initiated the Medical Information for Risk Assessment Initiative (MIHARI) project to develop a new drug safety assessment framework based on RWD.<sup>20</sup> Since then, the PMDA has actively conducted pharmaco-epidemiological studies based on RWD, such as insurance claims, electronic medical records (EMRs), and the Diagnosis Procedure Combination (DPC) system, which is a comprehensive inpatient reimbursement system analogous to the US diagnosis-related group system.<sup>20</sup>

**Table 3** summarizes the recent pharmaco-epidemiological studies based on RWD conducted by the PMDA. The data sources for the studies were the Japanese National Claims Database (NDB) or MID-NET®. The NDB is a nationwide database in Japan operated by the MHLW, and contains the electronic claims data covering almost all Japanese individuals (~120 million) and special health check-up data since April 2009.<sup>21</sup> MID-NET® is a new medical information database network that is known to be a reliable and valuable database in Japan and stores EMRs, administrative claim

data, and DPC data of over 5.3 million patients (as of December 2020) in cooperation with 10 healthcare organizations, including 23 university hospitals or core regional hospitals.<sup>22</sup>

The purpose of these studies was to investigate the actual drug use or safety risks associated with a drug in clinical practice. We usually target not only one drug but similar types of other drugs for their pharmacological action related to the same indication, to examine the possibility of class effects on the risk targeted in a study. In particular, we conducted a study in a case where assessment based on spontaneous adverse event reports and other information made it difficult to determine the causal relationship between a drug and risk, and a quantitative approach was required for regulatory consideration.

An example is a nested case-control study to investigate the association between G-CSF preparations (filgrastim, nartograstim, lenograstim, and pegfilgrastim) available in Japan and thrombocytopenia in patients treated with antineoplastic agents.<sup>23</sup> The study revealed a significantly increased risk of thrombocytopenia associated with pegfilgrastim, leading to regulatory action to revise the package inserts of this drug.<sup>24</sup> Some of these studies also included cases where no additional safety measures were required, such as those for investigating retinal detachment associated with fluoroquinolone,<sup>25</sup> cardiovascular risks associated with drugs for hyperuricemia,<sup>26</sup> and abnormal renal function associated with

**Table 3 List of RWD-based studies on drug safety assessment conducted by the PMDA**

Research purpose (target events)	Target drugs	Data source	Summary of results and regulatory actions (decisions)
Prescription survey	Triptan	NDB	<ul style="list-style-type: none"> <li>A certain number of patients were suspected of overusing triptans</li> <li>Used as a reference for revising the package insert with more precautions</li> </ul>
Blood coagulability	DAAs ( <a href="https://doi.org/10.1007/s43441-020-00247-8">https://doi.org/10.1007/s43441-020-00247-8</a> )	MID-NET®	<ul style="list-style-type: none"> <li>Improvement of the liver function by DAAs might be related to the fluctuation in blood coagulability in patients receiving both DAA and warfarin</li> <li>Used as a reference for revising the package insert with more precautions</li> </ul>
Prescription survey	Valsartan	NDB	<ul style="list-style-type: none"> <li>Identified approximate number of patients, periods and doses of prescriptions</li> <li>Confirmed that no new additional safety measures were required</li> </ul>
Thrombocytopenia	G-CSF ( <a href="https://doi.org/10.1002/cpt.2263">https://doi.org/10.1002/cpt.2263</a> )	MID-NET®	<ul style="list-style-type: none"> <li>Increased risk of thrombocytopenia by pegfilgrastim</li> <li>Used as the major evidence for revising the package insert with more precautions</li> </ul>
Renal dysfunction	DAAs	MID-NET®	<ul style="list-style-type: none"> <li>Observed different risks of renal dysfunction among DAAs</li> <li>Confirmed that the current warning on the package insert was appropriate and no new additional safety measures were required</li> </ul>
Retinal detachment	Fluoroquinolone antibiotics	NDB	<ul style="list-style-type: none"> <li>Observed no increased risk of retinal detachment by fluoroquinolone</li> <li>Confirmed that no new additional safety measures were required</li> </ul>
Cardiovascular events	Anti-hyperuricemia drugs	NDB	<ul style="list-style-type: none"> <li>Observed no increased cardiovascular risk by anti-hyperuricemia drugs</li> <li>Confirmed that no new additional safety measures were required</li> </ul>

DAAs, direct-acting antivirals against hepatitis C; NDB, Japanese National Claims Database; PMDA, Pharmaceuticals and Medical Devices Agency; RWD, real-world data.

direct-acting antivirals.<sup>27</sup> Even in such cases, it provides more confidence about the adequacy of the present safety measures in real situations of clinical practice. Therefore, whether the study results are directly linked to safety measures or not, RWE enhances our understanding of the characteristics of drug safety and contributes to appropriate regulatory actions for drug safety.

**Table 4** shows the ongoing studies on drug safety assessment based on RWD conducted by the PMDA.<sup>28</sup> Many of these studies are planned for using MID-NET<sup>®</sup> to target various safety risks, such as cytopenia and hypocalcemia, in addition to liver function, and will provide RWE for contributing to the better drug safety assessment. The PMDA is currently working on the new use of MID-NET<sup>®</sup> data for safety signal detection/strengthening, which are planned to be started in early 2022. It will focus more on an early stage of drug safety assessment, even in a situation where no safety concerns are identified, rather than the later stage for signal confirmation where current studies focused. It is expected to detect safety signals earlier and contribute to more prompt safety measures for a drug.<sup>20</sup>

In addition, the PMDA has also led the research in collaboration with academia on validation studies of outcome definitions for promoting appropriate database study with a validated outcome, which is stated as an important consideration in the guideline titled “Basic principles in conducting a validation study on outcome definitions used for post-marketing database study”<sup>29</sup> (see also #10, in **Table 1**).

For pharmaceutical industries, the PMDA has conducted scientific consultations on planning the pharmacovigilance of an individual drug, including advice on study protocols and analytical methods. In planning the risk management plan of a drug, considerations about pharmaco-epidemiological studies utilizing RWD are encouraged to provide the necessary scientific data on target safety more appropriately and efficiently in a timely manner after drug approval. The list of actual cases utilizing MID-NET<sup>®</sup> as the postmarketing study conducted by pharmaceutical industries is available at the PMDA website.<sup>30</sup> Some of those are conducted in replacement of the traditional observational studies based on primary data collection.

## CHALLENGES IN UTILIZING RWD/RWE IN THE REGULATORY SETTING

As described above, the PMDA has accumulated our regulatory experiences on the utilization of RWD/RWE for regulatory decision making. The past experiences were mainly on drug safety assessment at the postmarketing stage and about the efficacy evaluation of orphan drugs. In addition, discussions regarding the acceptability of RWD and RWE for regulatory submission in the scientific consultation meetings have recently increased.

Based on these experiences, we recognized two important premises to use RWE for regulatory decision making (**Figure 2**). The first factor is the reliability and quality of the RWD in terms of accuracy, consistency, and completeness. The problematic cases resulting in the retraction of published articles due to a lack of data reliability have been recently reported.<sup>31,32</sup> RWD should be appropriately managed to provide adequate quality data for the study of regulatory submissions. In this regard, the guideline on data

reliability entitled “Points to consider for ensuring the reliability of post-marketing database study for drugs (medical devices/ regenerative medical products)” was published in 2018 to draw further attention and guide practical considerations on data reliability in utilizing RWD (see also #6, in **Table 1**). It should be noted that information regarding the features and data management practices of RWD should be available to users before initiating an RWD-based study. The second factor is the appropriateness of the analytical methods used in a study. This should be based on the latest scientific knowledge and consider the RWD characteristics. If one of these factors is missing, the results will be uninterpretable and may cause confusion in the society, that should really be avoided.

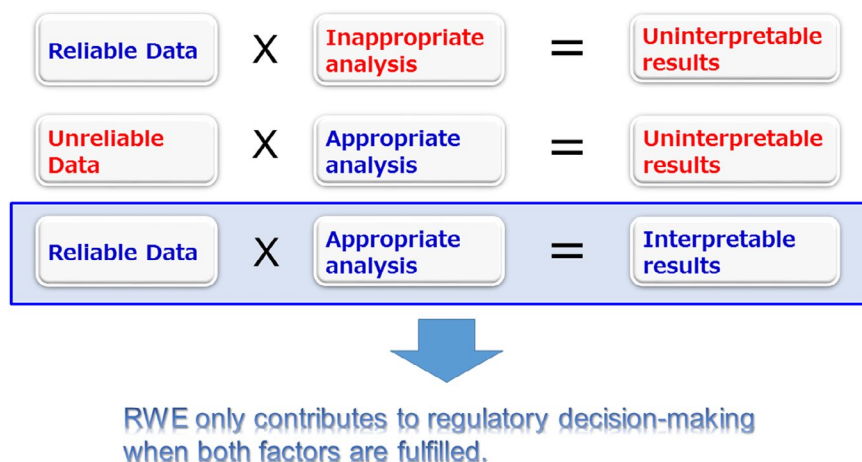
Practically, the required level of data reliability and the range of the required data differ depending on the purpose of utilization, such as how RWD is used for evaluation or assessment in the regulatory setting (e.g., postmarketing surveillance, external control of clinical trials, or supplementary information). To avoid incorrect interpretation or erroneous conclusions about the benefit/risk of a drug, RWD should be utilized with a good understanding of the circumstances, such as data characteristics and management, to ensure that it fits for the purpose of the study. Even in the case where data reliability and analytical methods were ensured, if actually collected RWD were unexpectedly less or limited, such data may not be used as a major evidence for regulatory decision making. Therefore, it is encouraged that pharmaceutical industries and/or data holders have discussions with the PMDA in advance in terms of utilization strategy, especially in cases where RWD is to be used as a major evidence for evaluating the efficacy and safety of a drug, including discussions about positioning of RWD in the clinical data package for new drug application or data sufficiency for postmarketing re-examination, appropriateness of the study protocol and analytical plan, and data reliability of RWD. Any regulatory issues in utilizing RWD should be shared and discussed to understand the critical issues regarding the acceptance of the study results based on RWD. As described above, the PMDA provides various scientific consultation programs at both pre- and postmarketing stages for active discussions on RWD and RWE. More experiences about RWD utilization in real cases through such activities facilitates a common understanding of the characteristics of RWD, including limitations for better RWD utilization in regulatory setting and are useful to find out a practical solution.

From now, the use of RWD in regulatory setting will be more diversified in terms of utilization purposes and data types.<sup>1,33</sup> For RWD utilization at the pre-approval stage, orphan diseases would be one of the major areas in utilizing RWD as a historical control, because it is generally difficult to conduct a randomized clinical trial. However, we expect that target disease area and purpose of RWD utilization at the pre-approval stage could be more varied. For example, RWD can be utilized not only in orphan diseases but also in other diseases, including common diseases for evaluating efficacy and/or safety of an investigational drug. At the postapproval stage, we expect to increase postmarketing studies based on secondary utilization of RWD under pharmacovigilance activities. Types of RWD could be also varied, including registry, EMRs, and other health-related information. RWE based on foreign RWD can be submitted to Japan,

**Table 4** List of on-going RWD-based studies on drug safety assessment conducted by the PMDA

Research purposes (target events)	Target drugs	Data source
Liver dysfunction	Drugs for pulmonary arterial hypertension	MID-NET®
Implementation status of the laboratory test on granulocyte counts	Thiamazole	MID-NET®
Exploring risk factors for decreased granulocyte counts	Thiamazole	MID-NET®
Digestive tube obstruction	Antipsychotic therapy	MID-NET®
Prescription survey	Biosimilars	MID-NET®
Impacts of revision on the package insert relating to lactic acidosis	Metformin	MID-NET®
Hypocalcemia in patients with renal dysfunction	Bisphosphonates	MID-NET®
Prescription survey	Metformin	NDB
Liver dysfunction	ACE inhibitors	MID-NET®
Thrombocytopenia	Antidepressants	MID-NET®
Neutropenia	Drugs for psoriasis	MID-NET®

ACE, angiotensin converting enzyme; NDB, Japanese National Claims Database; PMDA, Pharmaceuticals and Medical Devices Agency.



**Figure 2** Prerequisite of RWE contributing to regulatory decision making. RWE, real-world evidence.

although applicability of RWD to Japan and impacts of ethnic factors on results should be considered and be discussed with the PMDA in advance. In these situations, the development of more guidelines on RWD/RWE in Japan, such as general principles and data reliability standards for medical database utilization for new drug applications, is expected in the near future. Updating the existing guidelines would also be necessary for a timely response to scientific advancement based on accumulated experiences. In April 2021, the PMDA established the RWD working group, which comprises multidisciplinary PMDA experts from various offices, such as new drug review, safety, nonclinical and clinical compliance, medical informatics and epidemiology.<sup>8</sup> The RWD working group discusses all regulatory issues relating to RWD/RWE, such as data reliability standards and methodological approaches, and promotes the utilization of RWD in Japanese pharmaceutical regulations. This group also plays an active role in sharing knowledge and experiences not only within the MHLW/PMDA, but also with the stakeholders, including pharmaceutical industries, academia, and foreign regulatory

agencies. Regulatory acceptance of new technologies, such as data collection by wearable devices and data handling and screening by artificial intelligence, would also be discussed. The PMDA welcomes more discussions and proposals on new regulatory issues that might not be covered in the existing guidelines.

Another challenge in RWD/RWE is the international harmonization of regulatory requirements. Different regulatory requirements on RWD/RWE among countries/regions might create another hurdle in promoting its utilization and make it difficult to share RWE globally. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has started to discuss RWD/RWE-related topics, including Good Clinical Practice renovation.<sup>34</sup> Pharmaco-epidemiology discussion group of the ICH (PEpiDG) has also started to discuss what kinds of ICH guidelines are necessary and high priority for promoting efficient drug development and pharmacovigilance with a view to pharmaco-epidemiological study based on RWD.<sup>35</sup> In June 2021, the ICH assembly supported the proposal by PEpiDG for establishing

a new ICH guideline on the general principles for planning and designing pharmaco-epidemiological studies that utilize RWD for safety assessment of a medicine.<sup>36</sup> The International Coalition of Medicines Regulatory Authorities (ICMRA) has also shared regulatory experiences utilizing RWE, such as observational studies on coronavirus disease 2019 (COVID-19).<sup>37</sup> Global sharing of accumulated experiences not only among regulatory agencies but also with the pharmaceutical industry, data holders, and academia will be important for promoting international harmonization and establishing international standards that are scientifically reasonable and feasible in different countries/regions.

**CONCLUSION**

The PMDA will continue efforts to promote the appropriate utilization of RWD/RWE in a regulatory setting. We look forward to more discussions, international collaborations, and further accumulation of regulatory experiences aimed at popularizing the RWE-based benefit/risk assessment of a drug.

**ACKNOWLEDGMENTS**

The views expressed herein are the result of independent work and do not necessarily represent the views and findings of the Pharmaceuticals and Medical Devices Agency.

**FUNDING**

No funding was received for this work.

**CONFLICTS OF INTEREST**

The authors declared no competing interests for this work.

**AUTHOR CONTRIBUTIONS**

All authors equally contribute to the manuscript.

**PAST PRESENTATION ON THIS RESEARCH**

None.

© 2021 The Authors. *Clinical Pharmacology & Therapeutics* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

1. Sherman, R.E. et al. Real-world evidence - what is it and what can it tell us? *N. Engl. J. Med.* **375**, 2293–2297 (2016).
2. Cave, A., Kurz, X. & Arlett, P. Real-world data for regulatory decision making: challenges and possible solutions for Europe. *Clin. Pharmacol. Therapeut.* **106**, 36–39 (2019).
3. US Food and Drug Administration. Framework for FDA’s Real-World Evidence Program <<https://www.fda.gov/media/120060/download>> (2018). Accessed August 12, 2021.
4. US Food and Drug Administration. Guidance for industry and FDA staff: best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data <<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf>> (2013). Accessed August 12, 2021.
5. US Food and Drug Administration. Draft guidance for industry: submitting documents using real-world data and real-world evidence to FDA for drugs and biologics <<https://www.fda.gov/media/124795/download>> (2019). Accessed August 12, 2021.

6. European Medicine Agency. Guideline on registry-based studies (draft) <[https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en.pdf)> (2020). Accessed August 12, 2021.
7. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology <[http://www.encepp.eu/standards\\_and\\_guidances/documents/GuideMethodRev8.pdf](http://www.encepp.eu/standards_and_guidances/documents/GuideMethodRev8.pdf)> (2010). Accessed August 12, 2021.
8. Pharmaceuticals and Medical Devices Agency (PMDA), Real World Data Working Group (RWD WG). Overview of WG: List of guidelines <<https://www.pmda.go.jp/english/rs-sb-std/rs/0023.html> <<https://www.pmda.go.jp/english/rs-sb-std/rs/0023.html>> (2021). Accessed August 12, 2021.
9. Revising Japan Revitalization Strategy: [8] Construction of clinical innovation networks (Creation of clinical development infrastructure utilizing disease registration information), decision by Cabinet on June 30, 2015 <[https://www.kantei.go.jp/jp/singi/keizaisaisei/pdf/dai2\\_3en.pdf](https://www.kantei.go.jp/jp/singi/keizaisaisei/pdf/dai2_3en.pdf)> (2015). Accessed August 12, 2021.
10. Ministry of Health, Labour and Welfare. PSEHB/PED Notification No.0323-1/PSEHB/MDED Notification No.0323-1, Basic principles on utilization of registry for applications <<https://www.pmda.go.jp/files/000240806.pdf>> (2021). Accessed August 12, 2021.
11. Ministry of Health, Labour and Welfare. PSEHB/PED Notification No.0323-2/PSEHB/MDED Notification No.0323-2, Points to consider for ensuring the reliability in utilization of registry data for application <<https://www.pmda.go.jp/files/000240807.pdf>> (2021). Accessed August 12, 2021.
12. Ministry of Health, Labour and Welfare. Orphan drug designation system in Japan (Japanese only) <<https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000068484.html>>. Accessed August 12, 2021.
13. Murakami, M. & Narukawa, M. Matched analysis on orphan drug designations and approvals: cross regional analysis in the United States, the European Union, and Japan. *Drug Discovery Today* **21**, 544–549 (2016)
14. Pharmaceuticals and Medical Devices Agency (PMDA). Review report: alglucosidase-alfa (Genetical Recombination) <<https://www.pmda.go.jp/files/000153325.pdf>> (2007). Accessed August 12, 2021.
15. Pharmaceuticals and Medical Devices Agency (PMDA). Review report: argatroban hydrate (Japanese only) <[https://www.pmda.go.jp/drugs/2011/P201100089/400315000\\_21700AMZ00221\\_A100\\_1.pdf](https://www.pmda.go.jp/drugs/2011/P201100089/400315000_21700AMZ00221_A100_1.pdf)> (2011). Accessed August 12, 2021.
16. Pharmaceuticals and Medical Devices Agency (PMDA). Review report: asfotase-alfa <<https://www.pmda.go.jp/files/000213563.pdf>> (2015). Accessed August 12, 2021.
17. Pharmaceuticals and Medical Devices Agency (PMDA). Review report: tacrolimus hydrate (Japanese only) <[https://www.pmda.go.jp/drugs/2013/P201300087/800126000\\_20500AMZ00157000\\_A100\\_2.pdf](https://www.pmda.go.jp/drugs/2013/P201300087/800126000_20500AMZ00157000_A100_2.pdf)> (2013). Accessed August 12, 2021.
18. Pharmaceuticals and Medical Devices Agency (PMDA). Review report: viltolarsen <<https://www.pmda.go.jp/files/000237467.pdf>> (2020). Accessed August 12, 2021.
19. National Center of Neurology and Psychiatry Translational Medical Center. Remudy (Registry of Muscular Dystrophy) <<http://www.remudy.jp/english/>>. Accessed August 12, 2021.
20. Ishiguro, C., Takeuchi, Y., Uyama, Y. & Tawaragi, T. The MIHARI project: establishing a new framework for pharmacoepidemiological drug safety assessments by the Pharmaceuticals and Medical Devices Agency of Japan. *Pharmacoepidemiol. Drug Saf.* **25**, 854–859 (2016).
21. Komamine, M., Kajiyama, K., Ishiguro, C. & Uyama, Y. Cardiovascular risks associated with dipeptidyl peptidase-4 inhibitors monotherapy compared with other antidiabetes drugs in the Japanese population: a nationwide cohort study. *Pharmacoepidemiol. Drug Saf.* **28**, 1166–1174 (2019).
22. Yamaguchi, M. et al. Establishment of the MID-NET® medical information database network as a reliable and



- valuable database for drug safety assessments in Japan. *Pharmacoepidemiol. Drug Saf.* **28**, 1395–1404 (2019).
23. Kajiyama, K. *et al.* Nested case-control study utilizing MID-NET® on thrombocytopenia associated with pegfilgrastim in patients treated with antineoplastic agents. *Clin. Pharmacol. Ther.* **110**, 473–479 (2021).
  24. Pharmaceuticals and Medical Devices Agency (PMDA). Revision of the package insert of G-CSF preparations (Japanese only) <<https://www.pmda.go.jp/files/000234643.pdf>> (2020). Accessed August 12, 2021.
  25. Pharmaceuticals and Medical Devices Agency (PMDA). Summary results: pharmacoepidemiological study for investigating retinal detachment associated with fluoroquinolone (Japanese only) <<https://www.pmda.go.jp/files/000240294.pdf>> (2021). Accessed August 12, 2021.
  26. Pharmaceuticals and Medical Devices Agency (PMDA). Summary results: pharmacoepidemiological study for investigating cardiovascular risks associated with drugs for hyperuricemia (Japanese only) <<https://www.pmda.go.jp/files/000239435.pdf>> (2021). Accessed August 12, 2021.
  27. Pharmaceuticals and Medical Devices Agency (PMDA). Summary results: pharmacoepidemiological study for investigating abnormality of renal functions associated with DAAs (Japanese only) <<https://www.pmda.go.jp/files/000238109.pdf>> (2020). Accessed August 12, 2021.
  28. Pharmaceuticals and Medical Devices Agency (PMDA). Pharmacoepidemiological studies for drug safety assessment under MIHARI framework (Japanese only) <<https://www.pmda.go.jp/safety/surveillance-analysis/0045.html>>. Accessed August 12, 2021.
  29. Pharmaceuticals and Medical Devices Agency. Basic principles in conducting a validation study on outcome definitions used for post-marketing database study. Notification on July 31, 2021, No. 0731002 of Center for Regulatory Science & No. 0731002 of Center for Product Evaluation (Japanese only) <<https://www.pmda.go.jp/files/000235927.pdf>> (2020). Accessed August 12, 2021.
  30. Pharmaceuticals and Medical Devices Agency. Information about approved studies utilizing MID-NET® <<https://www.pmda.go.jp/safety/mid-net/0010.html>> (2021). Accessed August 12, 2021.
  31. Rubin, E.J. Expression of concern: Mehra MR *et al.* Cardiovascular disease, drug therapy, and mortality in covid-19. *N. Engl. J. Med.* DOI: <https://doi.org/10.1056/NEJMoa2007621>. *N. Engl. J. Med.* **382**, 2464 (2020).
  32. The Lancet Editors. Expression of concern: Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* **395**, e102 (2020).
  33. Schneeweiss, S. *et al.* Real world data in adaptive biomedical innovation: a framework for generating evidence fit for decision-making. *Clin. Pharmacol. Therapeut.* **100**, 633–646 (2016).
  34. ICH reflection on “GCP renovation”: modernization of ICH E8 and subsequent renovation of ICH E6 <[https://admin.ich.org/sites/default/files/2019-04/ICH\\_Reflection\\_paper\\_GCP\\_Renovation\\_Jan\\_2017\\_Final.pdf](https://admin.ich.org/sites/default/files/2019-04/ICH_Reflection_paper_GCP_Renovation_Jan_2017_Final.pdf)> (2017). Accessed August 12, 2021.
  35. ICH Reflection paper: strategic approach to international harmonization of technical scientific requirements for pharmacoepidemiological studies submitted to regulatory agencies to advance more effective utilization of real-world data <[https://admin.ich.org/sites/default/files/2019-08/ICH\\_ReflectionPaper\\_Pharmacoepidemiology\\_2019\\_0605.pdf](https://admin.ich.org/sites/default/files/2019-08/ICH_ReflectionPaper_Pharmacoepidemiology_2019_0605.pdf)> (2019). Accessed August 12, 2021.
  36. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Press Release: ICH Assembly Virtual Meeting June 2021 <<https://www.ich.org/pressrelease/press-release-ich-assembly-virtual-meeting-june-2021>> (2021). Accessed August 12, 2021.
  37. International Coalition of Medicines Regulatory Authorities, COVID-19 <<http://www.icmra.info/drupal/en/covid-19>> (2021). Accessed August 12, 2021.