Japanese Regulatory Perspective

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Regulatory Actions to Encourage Real-World Data (RWD) Utilization in Japan

2018 MHLW revised the Ministerial Ordinance to utilize RWD in post-marketing surveillance(PMS).

2019 PMDA has launched registry consultations.

2021 MHLW issued guidance for the utilization of registry.

Guidance reference;
“Basic principles on Utilization of Registry for Applications”: PSEHB/PED Notification No.0323-1, PSEHB/MDED Notification No.0323-1, March 23, 2021
“Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications”: PSEHB/PED Notification No.0323-2, PSEHB/MDED Notification No.0323-2, March 23, 2021

Facing Challenges of Utilizing RWD for Regulatory Decision-Making of Medical Devices

1. How can we accelerate medical device development by utilizing RWD?
2. What are the principles of reliability of RWD?
3. What makes possible to achieve sustainable RWD collection?

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Case1: Strategy for Establishing Clinical Evidence by Post-Market Registry Data

Post-market RWD can be potential RWE to change indication.

Agent Paclitaxel-coated Balloon Catheter (Boston Scientific Japan K.K., approved in 2022)

Indication：

It is used to inhibit restenosis in revascularization for coronary in-stent restenosis and de novo coronary lesions. *For de novo lesions with a control vessel diameter of 3.0 mm or more, this product should be used only in patients who are judged to be suitable for treatment with this product compared with stent placement.*

Vessel diameter	ISR	de novo
2.0～3.0 mm	●	●
3.0～4.0 mm	●	★

Pre-market evaluation using AGENT Japan Trial

Limited pre-market evidence

- ✓ **DCB for de novo large vessel lesions** are treated along with an official statement* issued by the academic society(CVIT).
- ✓ For treatment with these lesions, **registration in the ALLIANCE registry is needed**.

*https://www.cvit.jp/_assets/documents/news/2023/0104.pdf

Muramatsu T, et al., Cardiovascular Intervention and Therapeutics (2023) 38:166–176

Case 2: Utilization of Registry Data as Substitute for Clinical Study

International registry data is a candidate for pre-market clinical evidence

Product name	Indication (underlined indication was added)
Edwards SAPIEN 3 (Edwards Lifesciences Limited, approved in 2022)	Patients with symptomatic valvular disease due to failing (stenosed, insufficient, or combined) of a surgical or **transcatheter** bioprosthetic aortic valve who are not eligible for surgery and of which treatment with SAPIEN 3 is considered as their best therapeutic option.

- There is growing **medical need** of treatment by **TAV in TAV** in Japan.
- It is difficult to conduct a clinical study because of **a limited number of patients and characteristics of patient population**.
- The applicant utilized **TVT registry data as a primary source of clinical outcomes.**

- ✓ **Some information of TVT registry is deleted** when the data are transferred to the applicant, **but the applicant can complement the information** with another data set.
- ✓ **The reliability of the registry data in the approval application document was confirmed**.

The review report is available in English: https://www.pmda.go.jp/files/000251033.pdf

Case 3: Efficient Post-Marketing Surveillance Using the Registry Platform of an Academic Society

Utilizing RWD may be one of the solutions for efficient PMS.

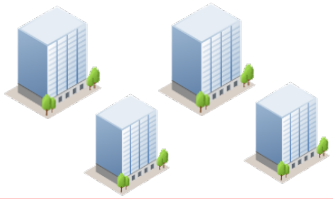
Woven EndoBridge
(Terumo Corporation) July 2020-

PulseRider
(Johnson & Johnson K.K.) July 2020-

Pipeline Flex FD*
(Medtronic Japan Co., Ltd.) March 2021-

Surpass Streamline FD*
(Stryker Japan K.K.) October 2021-

Industries



Data provision

Contract

PMS application

Consultation

JSNET

Academia

Consultation

Pmda

Regulatory

- ✓ **JSNET constructed PMS registries** of **implant devices for cerebral aneurysms**.
- ✓ The academic society **has the necessary experience** to construct these registries efficiently.

Photos are From the Web Page of Terumo.co.jp, PMDA and Am J Neuroradiol Jan 2016, 37:130 –35
Reference URL: http://jsnet.website/documents.php?id=780, *FD means Flow Diverter system

Case 4: Utilizing RWD to Promote Development of Medical Devices for Children/Rare Diseases

Post-market clinical evaluation using RWD may be an important option for devices with developmental difficulties.

- Devices approved for pediatric/rare diseases from 2008 to 2019 in Japan represent **only 7%** of all devices.
- **The burden for industries is critical,** because the market is too small.
- **Balancing the pre- and post-market clinical evaluation through the lifecycle of devices utilizing RWD is an important strategy.**

AMPLATZER Piccolo Occluder
(Abbott Medical Japan Co., Ltd.) June 2020-

Prosthetic Material for Vessel Embolization in patients with patent ductus arteriosus（PDA） including low birth weight infants ➡ **PMS using JCIC registry**

- ✓ **The academic society optimized original database to become a registry for PMS.**
- ✓ **We continue to discuss how to utilize JCIC registry for PMS of other endovascular devices.**

Takahashi S, et al., *J Artif Organs*. **2021,** 24, 90-101.
https://www.nibiohn.go.jp/nibio/part/promote/files/ph_orphanlist_medicaldevice_JP.pdf
http://www.jpic-meeting.org/pdf/4th_Amplatzer_final.pdf

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Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications

MHLW issued guidance about points to consider for ensuring data reliability of registries as clinical data in approval application documents.

- Since registry data is collected according to the original purpose of registries, **the concepts and methods adopted to ensure reliability of registry data vary**.
- The level of reliability required for the registry data may vary **depending on the purpose of utilization.**
- **An applicant is encouraged to consult PMDA** regarding necessary matters to ensure the reliability of registry data in application documents.

PSEHB/PED Notification No.0323-2, PSEHB/MDED Notification No.0323-2, March 23, 2021
https://www.pmda.go.jp/files/000240807.pdf

Consultations for Development and Utilization of Registry

PMDA has launched two consultation services regarding the reliability of registry data for medical devices.

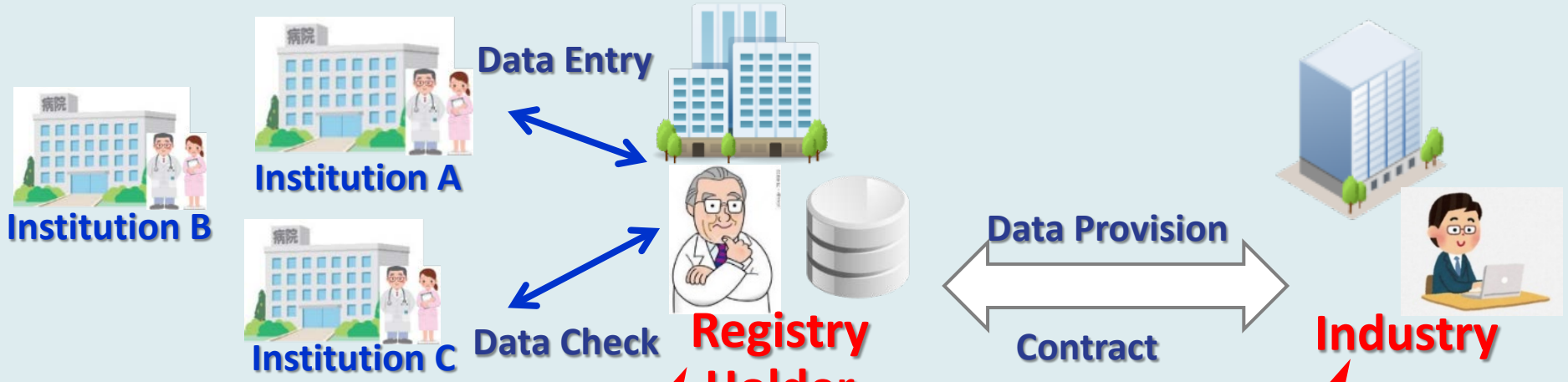
Number of cases* **(FY2019~FY2022)**

	Consultation Category	Consulter	Objective	
1	**Consultation on Registry Utilization**	**Registry holder (mainly academic society)** 	- General consideration of development strategies for registry - Methods of ensuring the data reliability of registry for marketing approval/PMS applications	4
2	**Consultation on Compliance Assessment of Registries**	**Industry** 	- Check and specify the status of data reliability of registry for marketing approval/PMS applications corresponding to an individual new device	4

*https://www.pmda.go.jp/files/000263261.pdf

Materials for Registry Consultations

PMDA conducts these consultations at different stages of development.



Consultation on Registry Utilization

- Quality control and quality assurance
- Data analysis
- Preservation of records
- Operating procedures etc.

https://www.pmda.go.jp/files/000219237.pdf

Consultation on Compliance Assessment of Registries

- Selection of registry
- Contract with registry holders
- Quality control
- Data analysis
- Preservation of records
- Operating procedures
- Study protocol (if applicable) etc.

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Discussion items for sustainability of RWD utilization

It is necessary for global stakeholders to discuss acceleration of RWD utilization.

✓ **For the highly-usable registry;**
- Essential endpoints and appropriate evaluation period
- Not biased in patient selection
- Globally-harmonized terms, definitions, and assessment methods

✓ **For the reliability of data;**
- Fit for purpose
- Discussion with PMDA
- Novel and efficient way to confirm the reliability data of international RWD

✓ **For the sustainable registry;**
- Minimizing endpoints
- Reusable or versatile for related devices/other type of devices
- Resource(human resource, financial resource)
- Strategic approach for utilizing pre-market evaluation

Conclusion

1. The collaboration between stakeholders is important to accelerate the utilization of RWD

2. We need to continue discussing for more effective RWD utilization in regulatory decision making