厚生労働省 ひと、くらし、みらいのために Ministry of Health, Labour and Welfare

Utilization of Real World Data for Marketing Authorization of Drugs

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Background (1)

Clinical trial and Real World Data

- Clinical trials are conducted to prove the efficacy and safety of a treatment to obtain marketing approval. These studies are carefully planned and conducted in a controlled environment, with an appropriate control group, and a carefully chosen patient population. Randomization is also used to eliminate bias. Such stringent planning of clinical trials helps to establish a causal relationship between the treatment and its effect, ensuring comparability with the control and data quality, which reduces the risk of making a wrong decision.
- There are some diseases with unmet medical needs, and drugs or other medical products haven't been developed for them due to a very limited patient population. This makes conventional trial-based development challenging.
- As a result, exceptional practices in clinical development are required to facilitate the development of drugs for such diseases.

Background (2)

Real World Data in Japan

- The utilization of Real World Data (RWD) obtained in the actual medical environment is gaining momentum in the development of drugs and medical devices globally.
- Various registries such as MID-NET by PMDA have already been established in Japan. The use of such registries and other RWD can help demonstrate and evaluate the efficacy and safety of treatment with data obtained from shorter-term and lower-cost clinical trials with fewer patients instead of conventional clinical trials.

- To facilitate the utilization of RWD for the development of drugs
  - ① Published Guidance notifications; the “Basic Principles on Utilization of Registry for Applications” and “Points to Consider for Ensuring the Reliability in Utilization of Registry Data for Applications”
  - ② Set-up Consultation services

Notifications on RWD: Basic Principles (1)

"Basic Principles on Utilization of Registry for Applications"
(PSEHB/PED Notification No.0323-1, PSEHB/MDED Notification No.0323-1, March 23, 2021)

Scope of the notification

- The Basic Principles shall apply to cases where registry data are utilized mainly in documents of clinical data on items included in the applications or notifications, such as application for approval and revision of package inserts, for drugs, medical devices and regenerative medical products submitted in accordance with the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Product, and Cosmetics (PMD Act)
- The principles are partially applicable to cases where data in the placebo group in the previous trials are utilized.
- The principles are also partially applicable to efficacy and safety evaluation for the applications, using data from medical records, and the applicants are strongly encouraged to refer to this notification and discuss the applicability beforehand using the consultation service offered by PMDA.

*English translation of the notification: https://www.pmda.go.jp/files/000240806.pdf

Notifications on RWD: Basic Principles (2)

"Basic Principles on Utilization of Registry for Applications"
(PSEHB/PED Notification No.0323-1, PSEHB/MDED Notification No.0323-1, March 23, 2021)

Data sources

- RWD sources include medical records, claims, disease registries, product registries of drugs and other medical products, and other healthcare data sources (such as data obtained from Home Use Devices and Mobile devices)

Challenges

- The utilization of RWD may facilitate the development of drugs for diseases which have been difficult for reasons such as a limited patient population. However,
  - ✓ Most RWDs are not optimized for use in the efficacy and safety evaluation
  - ✓ Data from medical records and claims are not necessarily collected or organized for research purposes
  - ✓ The quality of data should be considered when utilizing RWD for the evaluation of efficacy and safety to obtain market approval

Notifications on RWD: Basic Principles (3)

"Basic Principles on Utilization of Registry for Applications"
(PSEHB/PED Notification No.0323-1, PSEHB/MDED Notification No.0323-1, March 23, 2021)

Types of utilization of registry data for applications

1. Utilization of registry data in the investigation of feasibility at the planning of a clinical study
2. Utilization of registry data as an external control of clinical studies for efficacy and/or safety evaluation in applications
3. Utilization of registry data as a complement or substitute of a clinical study for efficacy and/or safety evaluation in applications.
4. Utilization of registry data in the evaluation of drugs and medical devices with conditional approval and of regenerative medical products with conditional and time-limited approval
5. Utilization of registry data in post-marketing efficacy and/or safety evaluation

Notifications on RWD: Basic Principles (4)

"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

- General points to consider
  1. Considerations for protection of personal information and patients' consent
  2. Reliability of registry data
  3. Appropriateness of registry data
  4. Early consultation with the registry holder
- For utilizing registry data as an external control of clinical studies, and For utilizing registry data for efficacy and safety evaluation
  1. Registry patient population
  2. Endpoints
  3. Evaluation period
  4. Statistical method
  5. Type of observational study for natural history (prospective or retrospective)

✓ **Applicants are (strongly) encouraged to discuss with PMDA**

Notifications on RWD: PtC for Ensuring Reliability (1)

"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)*

Purpose of the notification

- This notification indicates the points to consider for ensuring the reliability in utilization of registry data as a clinical data (evaluation data) for applications including application for marketing approval
- The scope of notification includes not only the registries to be newly constructed but also the registries that have been constructed with accumulated data

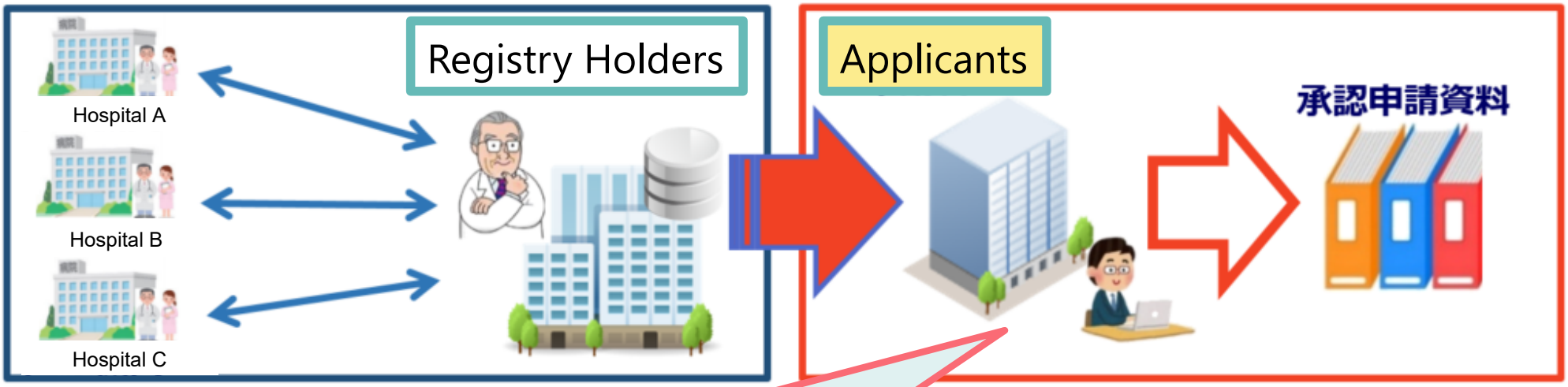
Concept of ensuring reliability

- Since registry data is collected according to the original purpose of registries, the concepts and methods adopted to ensure the reliability of registry data vary. The required level of reliability may also vary depending on the purpose of utilization of registry data.
- Therefore, an applicant is not required to ensure all the matters provided in this notification in a unified manner. But, an applicant is required to consider necessary matters on a case-by-case basis according to the purpose of utilization.
- An applicant is encouraged to consult PMDA to ensure the reliability of registry data.

*English translation of the notification: https://www.pmda.go.jp/files/000240807.pdf

Notifications on RWD: PtC for Ensuring Reliability (2)

"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)

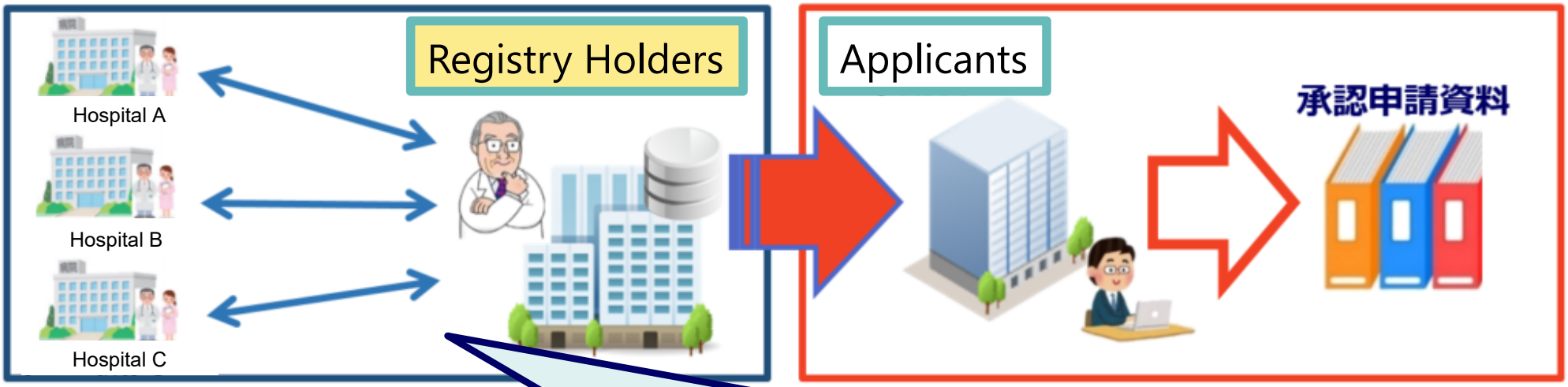


Applicants are required to comply with these matters when utilizing registry data

- Confirmation of data quality management implemented by registry holders
- Contract with registry holders
- Statistical Analysis in accordance with predetermined procedures and plans
- Preparation of data/documents for application in accordance with predetermined procedures
- Storage of record in accordance with predetermined procedures

Notifications on RWD: PtC for Ensuring Reliability (3)

"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)



Points to consider for the registry utilized as application data for marketing approval

- Governance
- Computerized system
- Quality Management of registry data
- Quality Assurance for registry
- Data extraction and Datasets preparation
- Protection of personal information and so on

Applicants should confirm the quality of registry data and determine whether the registry can adequately fulfil the intended purpose of utilization referring to these points to consider.

Support to Academia and Industries (1)

PMDA's Scientific advice for the usage of Registry

Consultation	Objective
Registry Utilization (Drugs, Regenerative medical products, Medical devices)	Provide general advice for the planning of registry utilization for applications, and advice for quality improvement and reliability assurance of registry intended to be utilized for applications ●For registry holders (University, Research institution etc.)
Registry Utilization Plan※ (Drug※※, Regenerative medicine)	Provide advice and direction for a plan to utilize a registry to evaluate the efficacy and safety of drugs or regenerative medicine on the validity of utilization, fulfilment of evaluation criteria, etc. ●(mainly) For marketing authorization holders
Registry Compliance Review (Drugs, Regenerative medical products, Medical devices)	Review and advice on the reliability of the registry to be utilized for applications before applications or compliance reviews ●(mainly) for marketing authorization holders

※" Consultation for the necessity of clinical trial of medical device " is available for medical devices

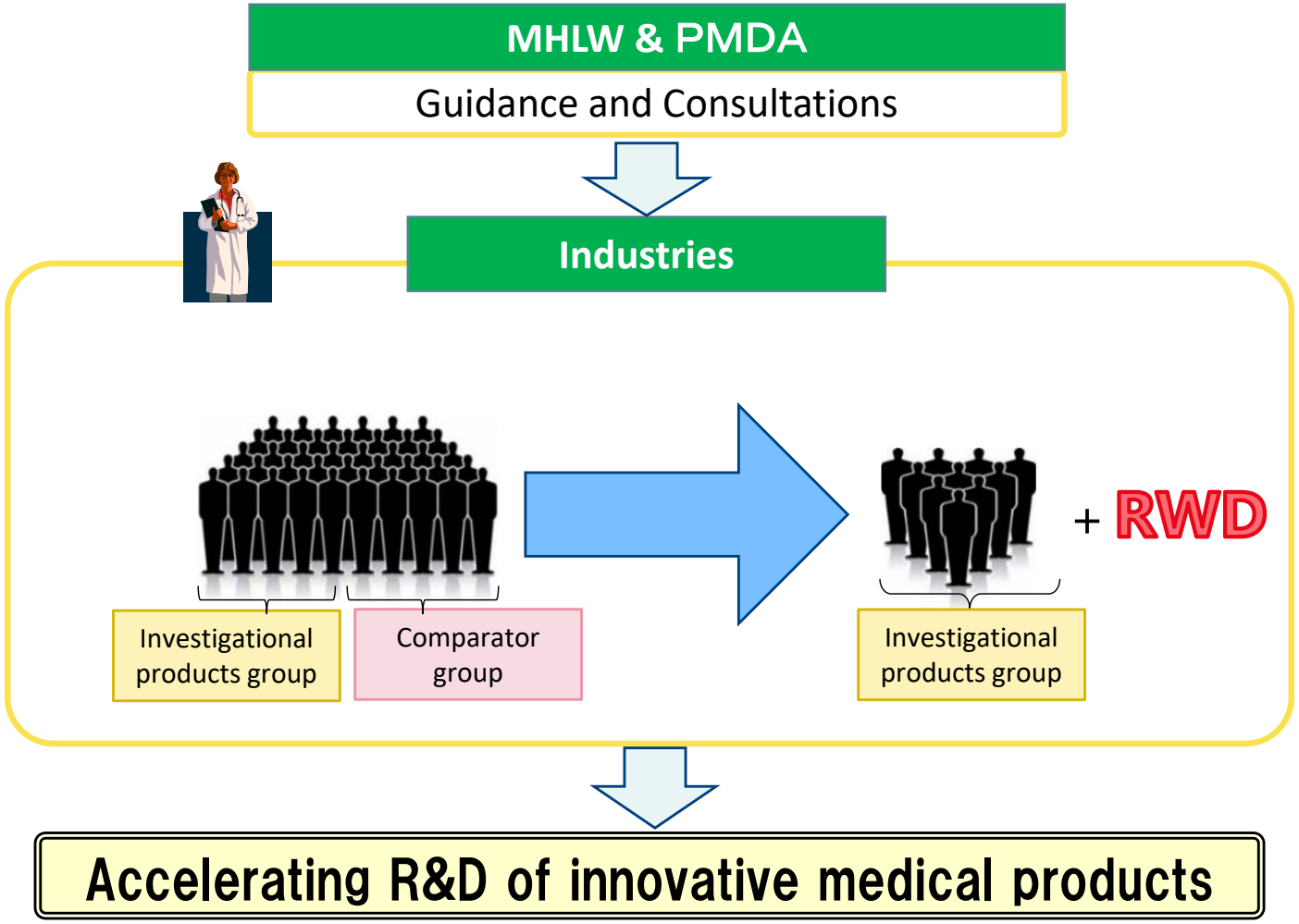
※※Other consultations for clinical trials of drugs are available for drugs

Support to Academia and Industries (2)

PMDA's Scientific advice for the usage of Medical Database

相談の種類	内容
Medical Database Utilization (Drugs)	Provide general advice for the planning of database utilization for applications and advice for quality improvement and reliability assurance of database intended to be utilized for applications ●(mainly) For Database provider
Medical Database Compliance Review (Drugs)	Provide advice for reliability assurance of medical database which will be utilized for applications before compliance review or conduct a compliance review ●(mainly) For marketing authorization holders
Epidemiological Survey (Drugs)	Provide direction and advice for a survey plan and procedures of post market survey of drugs ●(mainly) For marketing authorization holders

In conclusion



Thank you very much for your attention!