CMC Strategy Forum Japan 2019
Welcome and Introductory Comments

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Disclaimer: The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.
Center for Regulatory Science

- Pre-marketing stage
  - Review Offices
  - Office of Advanced Evaluation with Electronic Data (former Advanced Review with Electronic Data Promotion Group)
  - Office of Research Promotion
  - Office of Medical Informatics and Epidemiology
  - Safety Offices

- Post-marketing stage
  - Center for Regulatory Science
  - CDISC data
  - MID-NET etc.
Science Board

to close the gap between scientific innovation and product review

Collaboration

Academia
Universities, institutes, medical institutions

Exchange opinions between top-class researchers in Japan and PMDA reviewers on assessment methods of cutting-edge technologies
Example: Themes of Science Board

Subcommittee of Cellular and Tissue-based Products
(1st term: FY2012 – 2013)
Evaluate tumorigenicity of cellular and tissue-based products derived from induced pluripotent stem cells (iPSCs)

Subcommittee of Artificial Intelligence
Overview new technologies using AI and discuss their totally new characteristics in order to facilitate the future review and consultations on the products.

Subcommittee of Genome Editing
Assess the risk of genome edited products (The report expected in November 2019)
Subcommittee of Cellular and Tissue-based Products
Apr 2012 – Mar 2013

• Aim
  • Evaluation and appropriate management of the tumorigenicity of the final product due to residual / contaminated undifferentiated pluripotent stem cells in processed tissue products derived from pluripotent stem cells

• Considerations
  • Evaluation of tumorigenicity in processed tissue products derived from iPS cells etc. caused by contamination of undifferentiated and tumorigenic cells
  • Evaluation and management of tumorigenicity of human (allogeneic) iPS cells etc. used in the manufacture of processed tissue products

• Report
  • “Summary of discussion on tumorigenicity of processed tissue products manufactured based on iPS cells” Aug 20 2013
Subcommittee of Cell Processing Center
Apr 2014 – May 2016

• Aim
  • To sort out the issues and essential problems in the operation of CPC necessary to ensure the quality of regenerative medicine products manufactured using living cells.

• Considerations
  • Basic approach to quality assurance
  • Quality system concepts in manufacturing control and quality control.
  • Quality risk management
  • Educational training and knowledge management
  • Life cycle management
  • Verification
  • Respond to the latest technology

• Report
  • “Proposal on the basic concept for ensuring the quality of regenerative medicine products” Aug 14 2015
Subcommittee of Genome Editing
Apr 2018 – Mar 2020 (on going)

• Aim
  • To promote the development of safer genome editing technology and contribute to review of gene therapy products using genome editing by organizing the concept of risk assessment

• How to proceed
  • Classify and sort the characteristics according to the genome editing technology used and the technology for introducing it.
  • To summarize the considerations for safety based on the characteristics of genome editing technology.
  • Clarify the special considerations for genome editing during the clinical trial stage.
  • The way of thinking about risk assessment for gene therapy products using genome editing technology will be organized.
Subcommittee of Genome Editing - Considerations

- Quality issues
  - Classification by transfection method for genome editing
  - Classification by genome editing tools
  - Classification by the purpose of genome editing

- Safety issues in nonclinical studies
  - Ex vivo genome editing
    - Off-target effect, Unexpected genome deletion / unintended sequence insertion / chromosome translocation / inversion, p53 mutation in genome-edited cells
  - In vivo genome editing
    - Continuously expression over a long period of the editing enzyme may lead to increase in risk, Specificity to the target tissue / organ, Diverse genome editing tool introduction method and its safety

- Matters to be noted in clinical trials
  - Long term follow-up
Subcommittee of **Genome Editing**

- Progress and schedule

- Meeting
  - Nov. 8 2018
  - Dec. 25 2018
  - Feb. 26 2019
  - May 27 2019  Draft documentation
  - Oct. 29 2019  Acceptance by subcommittee
  - Nov. – Dec.  Acceptance by plenary committee

The document will be open on PMDA HP.
Assessment of benefit/risk of drugs based on RWD

Clinical Innovation Network (CIN)

- Study group for epidemiological methods and data quality standards
- Study group for ethical issues for registries and relationships with industries

About 20 members from New drugs & Safety Offices

MHLW

AMED

PMDA CIN-Working Group

Advice, Cooperation

Muscular dystrophy Registry by NCNP

ALS (Antilymphocytic serum) Registry by Nagoya Univ.

Cancer registry by National Cancer Center Japan

Cerebral surgery by Japan neurosurgical society

Output

Utilizing patient registry data for promoting cost effective clinical studies, quantitative B/R assessment and accelerating drug development
Assessment of benefit/risk of drugs based on RWD

- The Medical Information Database Network in Japan for a real-time assessment of drug safety
  - currently >4.7M patients
- PMDA has led the project for establishing an integrated real time EMRs database with high quality

MID-NET®

Medical Information Database Network

23 hospitals
Over 4.7 million patients in Japan
Assessment of benefit/risk of drugs based on RWD

Challenges in transforming RWD into RWE

- Data Quality Management (Reliability & Standardization)
- Appropriate PEpi Methods (Design & Analysis)

RWD (real world data) \neq RWE (real world evidence)

• The useful RWE can be obtained only under the following conditions.
  - Collection of RWD with high quality and standardization
  - Analyze data with appropriate study design and analytical methods
Roles of Center for Regulatory Science -Future Vision-

Past-Present

- Pilot/Cluster approach
  - Academic collaborations
  - CDISC data analysis
  - RWD utilization

4th MID-TERM plan (FY2019-FY2023)

- Unified approach as the center
  - More collaborations with academia and other regulatory agencies
  - Cross product analysis based on accumulated data for sophisticated review and consultation
  - More utilization of RWD for better benefit/risk assessment
  - More regulatory guidelines corresponding to the latest science
Example:
Expected outcome of e-DATA-based analysis

Pre-market

Feedback

• factors leading to successful drug development
e.g., ✓ factor for disease progression ✓ factor for PK variations

Review

Feedback

• factors on drug responses
e.g., ✓ factor for efficacy ✓ factor for safety

Feedback

Post-market

Feedback

• factors for promoting proper drug use
e.g., ✓ factor associated with adverse event ✓ factor for effectiveness

Collaborations with Academia for keeping up with the latest science

e-DATA-based regulation for maximizing an efficiency of drug development and ensuring the positive benefit/risk balance of a drug throughout product life cycle
Collaborations with Academia

CDISC-based assessment

RWD-based assessment

High quality service with the latest science

More integration of all regulatory science activities for efficient drug development and better pharmaceutical regulation

Advancing public health
Thank You

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