26G-ISMS44

Regulatory Science for R&D Promotion of Innovative Pharmaceuticals*

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BACKGROUND

At present the nation’s policy for research and development (R&D) promotion of innovative pharmaceuticals and improvement of environments for the R&D is formulated by Japanese government. In the policy, the enhancement and promotion of Regulatory Science (RS) touching the appropriate and rapid predict, evaluate, and judgment of quality, efficacy and safety of pharmaceuticals is especially stressed.

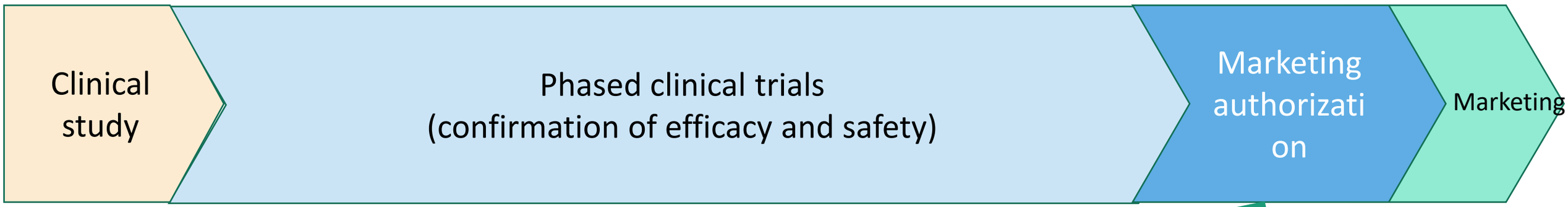
Following the nation’s policy, the Ministry of Health, Labor and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA), the National Institute of Health Sciences (NIHS), and Japan Agency for Medical Research and Development (AMED) are carrying out the activities to promote the R&D, cooperating with each other, academia, industry, or the other government bodies.

New expedited approval system under PMD Act - Conditional/term-limited authorization -

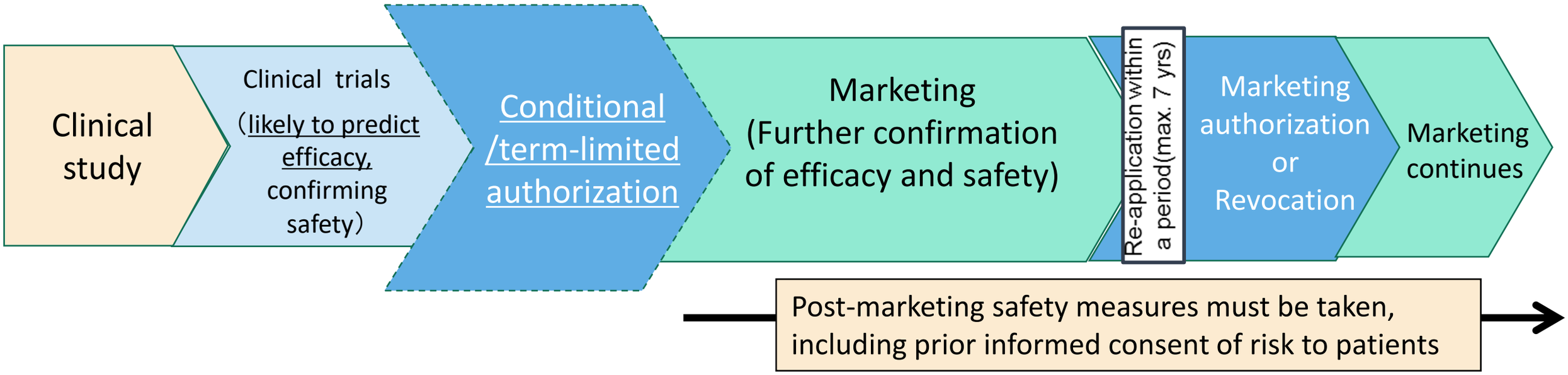
< Drawback of traditional PAL approval system >

<u>Long-term data collection and evaluation in clinical trials</u>, due to the characteristics of cellular/tissue-based products, **such as non-uniform quality** reflecting individual heterogeneity of autologous donor patients

[Traditional approval process]



[New scheme for regenerative medical products]



Two of the new product approvals under the new regulation (Update)

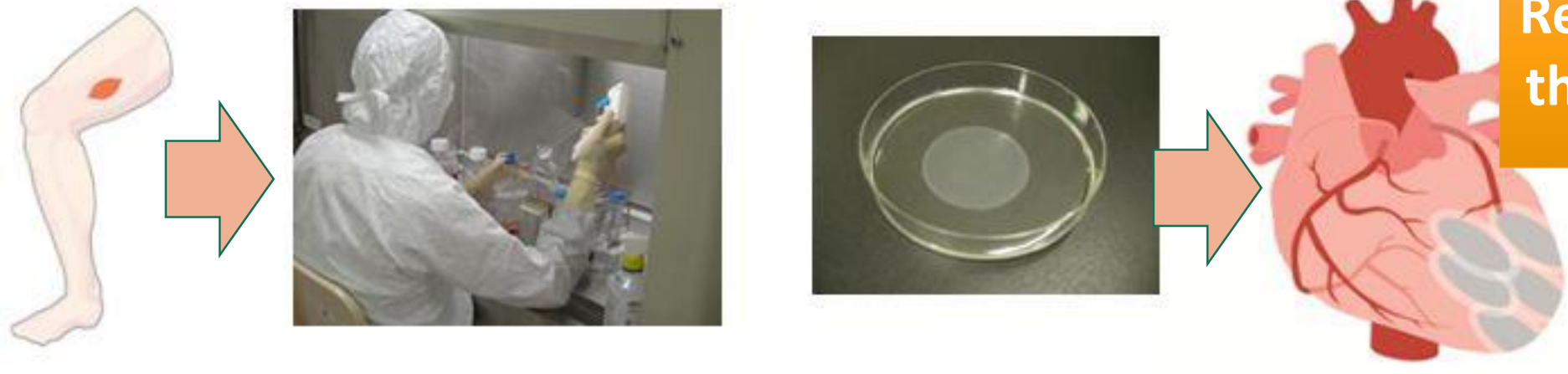
- In September and in October 2014, two new product applications for marketing authorization were filed by PMDA.
- They were approved on 18 September 2015.

1. Bone marrow mesenchymal stem cells (MSCs) for GVHD **(normal approval)**
2. Skeletal myoblast sheet for serious heart failure due to ischemic heart disease **(<u>conditional and time-limited authorization</u> – <u>5 years, conducting post-marketing efficacy studies</u>)**

Licensed by Mesoblast, Ltd.(Osiris Therapeutics, Inc.)

Conditional approval in Canada and New Zealand

Review Time less than 12 months)



Note: Figures quoted from the company press release docs

SAKIGAKE Designation System

SAKIGAKE is a system to put into practice innovative medicines/medical devices/regenerative medicines initially developed by Japan.

Designation Criteria

Medical products for diseases in urgent need of innovative therapy which may satisfy the following two conditions:

1. Having firstly developed in Japan and planned an application for approvals (desired to have PMDA consultation from the beginning of R&D)
2. Prominent effectiveness (i.e. radical improvement compared to existing therapy), can be expected based on the data of mechanism of action, non-clinical study and early phase of clinical trials (phase I to II)

Designation Advantage

: To shorten the time to approval

: To facilitate R&D

①Prioritized Consultation
[Waiting time: 2 months→1 month]
Shortening a waiting time for a clinical trial consultation from the submission of materials.

② Substantial Pre-application Consultation
[de facto review before application]
- Encouraging Consultation
- Accepting materials in English

③Prioritized Review
[12 months → 6 months]
Targeting total reviewing time: 6 months
* Accept the result of phase III study after the application on a case-by-case basis to shorten the time from R&D to approval

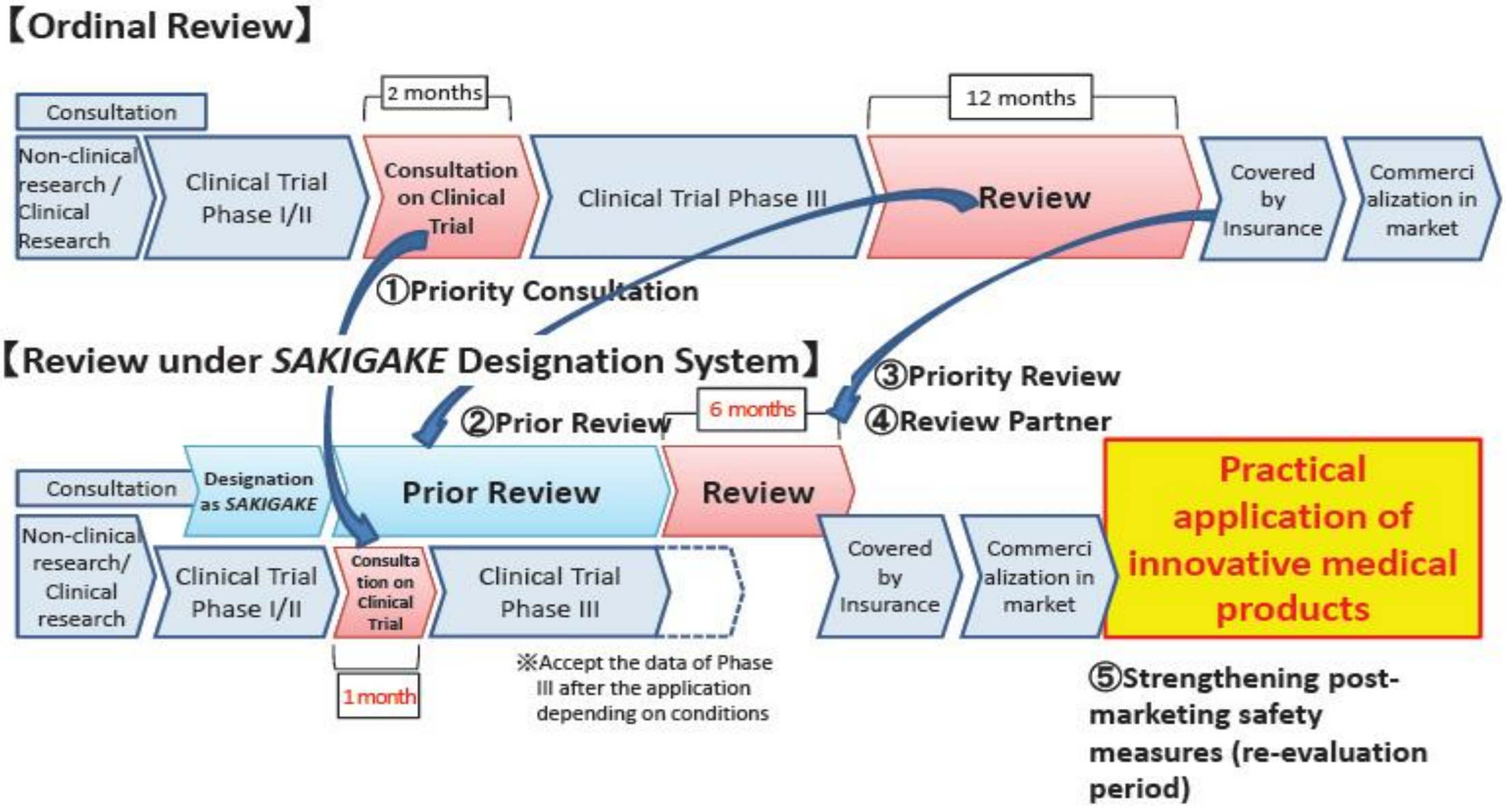
④Review Partner
[PMDA manager as a concierge]
Assign a manager as a concierge to take on overall management for the whole process toward approval including conformity assurance, quality management, safety measures, and reviewing application

⑤Substantial Post-Marketing Safety Measures
[Extension of re-examination period]
Strengthening post-marketing safety measures such as extension of re-examination period after approvals well as facilitating coalition with scientific societies, and global information dissemination.

Designation Procedure

1. **Option 1:** Application is to be submitted to Evaluation and Licensing Division (ELD) and to be reviewed by PMDA. The result of designation is to be notified within 60 days.
2. **Option 2:** ELD is to approach a potential applicant. The result of designation is to be notified within 30 days after the submission, if agreed by the applicant.

General Timeframe of *SAKIGAKE*



Accumulation and utilization of electronic-data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

Storage of electronic data in the dedicated server and registration in the database

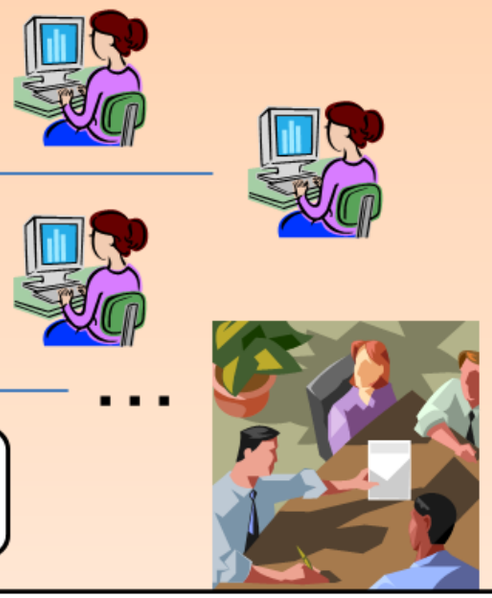
Visualization and analysis of data, supported by browsing software

Submission of electronic clinical study data has started since Oct 1st 2016!

Regulatory Review

Use of electronic data

- Accessible, visualized electronic data for each reviewer
- Easy to identify individual clinical case data, drilling down of data
- Operation of various analyses - simple, subgroup analysis for the present



Scientific discussion and decision making on the basis of internal analysis result

Utilization of Accumulated Data

Integration of cross-products information

- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab

Prospect of e-Study data utilization in Japan

Prospect As of Feb 2017
(Subject to Change)

Start e-study data submission for NDA* from Oct 1st, 2016

*NDA=New Drug Application

- e-study data can be received and managed appropriately
- e-study data can be utilized in the review
- Industries' workload is reduced gradually while keeping the review period

- J-FY2017

Setup e-data management and utilization

- More predictable efficacy/safety
- Consideration of expanding the scope of e-data utilization to toxicological study and post-approval clinical study

J-FY2018

Ordinary utilization of e-data in the product review

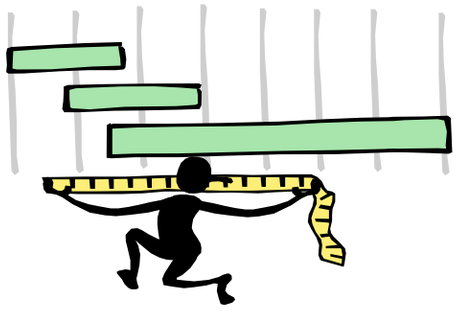
Promotion of paperless operation

Transitional period are taken until March 31st, 2020

- Preparations of guidelines and related documents
- Earnest on cross-product analysis and development of disease models

J-FY2019 - 2021

Starting earnest cross-product analysis

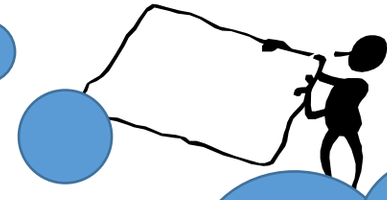


- Establishment of disease models
- Publication of disease-specific guidelines

J-FY2022 -

Publication of guidelines to contribute to drug development

First-class review authority

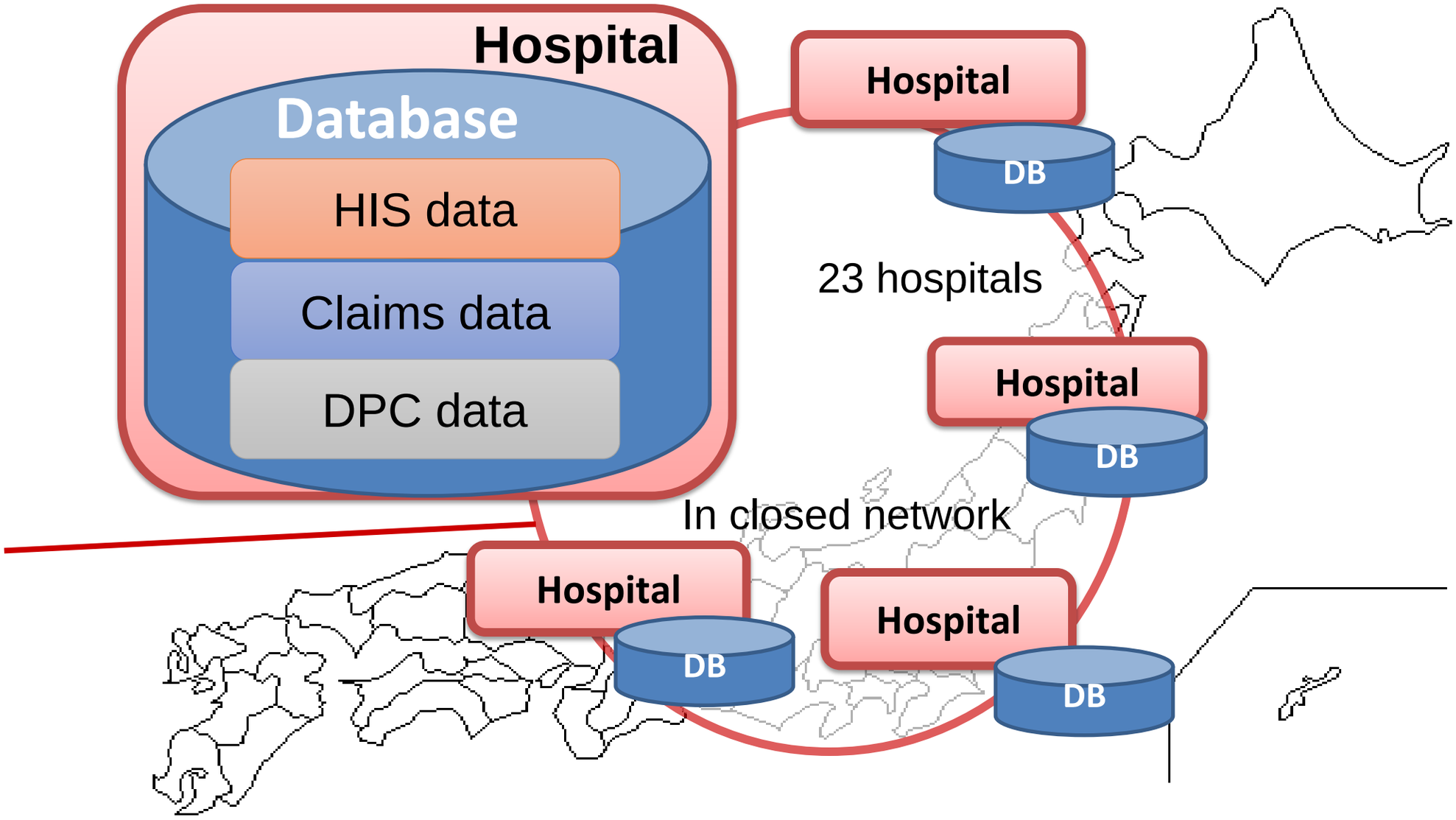


e.g. guidelines and disease models based on data on Asian population

MID-NET Project

- The Medical Information Database Network in Japan for a real-time assessment of drug safety (currently 4M patients)
- MID-NET will start full-scale service from 2018FY

PMDA

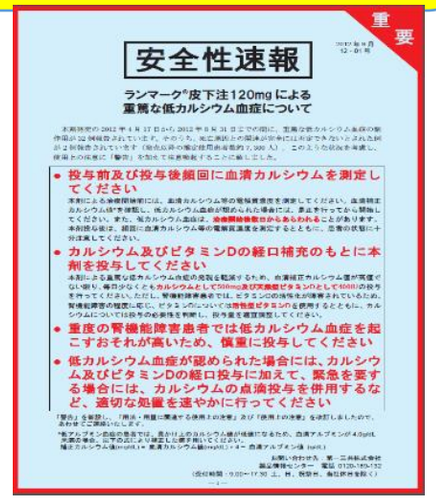


MID-NET will contribute to regulatory action
(Trial analysis: Denosumab for Hypocalcemia)

Launched
(2012.4.17)

Spontaneous ADR reports
(～2012.8.31)
- serious Hypocalcemia: 32 cases
- death:2 cases

Dear healthcare professionals letter
(2012.9.12)

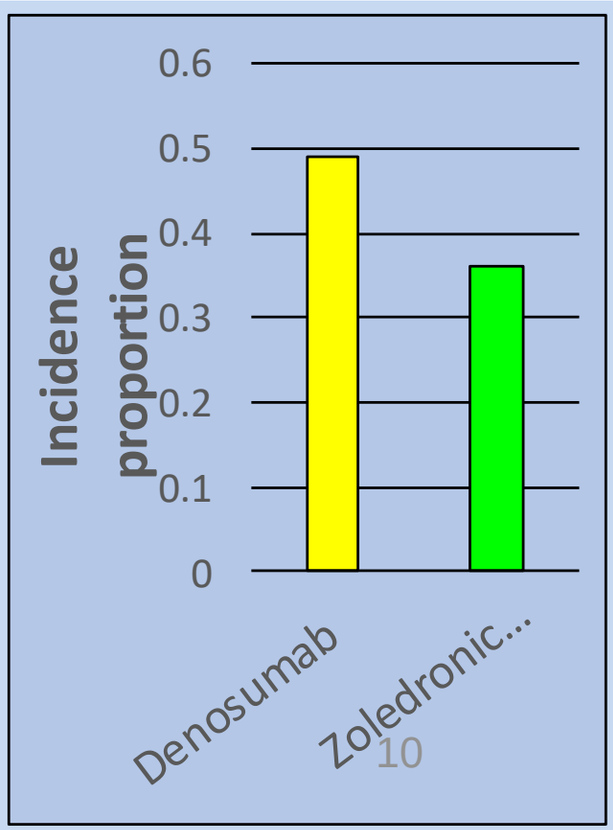


In near future

・Quantitative risk assessment compared with control

	Number of patients	Number of patient with Hypocalcemia	Incidence proportion	Relative risk
Denosumab	190	93	0.489	1.35
Zoledronic acid	245	89	0.363	

Data from 3 hospitals（2013/7～12）



PMDA Science Board

The Science Board was established in May 2012 to discuss how PMDA can better cope with products with advanced science & technology, in each developmental stage (basic research, development support, product review, and PMS).

Basic Research

Seeds of new drug / medical devices

Quality Tests → Non-clinical tests → Clinical Trial → Review → Approve → Post Marketing

Pharmaceutical consultation on R&D Strategy | Clinical Trial Consultation | Review | Post-marketing Safety Measure

Offices of Review (Drugs & Medical Devices), Office of Safety

Office of Regulatory Science

Practical use

Innovative medical products

Science Board

Topics in the 3rd term

1. Clinical evaluation of rare cancer
2. Facilitating R&D of Academia-originated Pharmaceuticals
3. Artificial Intelligence and its application in medical field

Board members

Communication

Academia (Knowledge of the Latest Innovative Technologies)

Regulatory Science for promoting cutting-edge medical products in National Institute of Health Sciences

AIM: Development and standardization of evaluation methods of cutting-edge pharmaceuticals, medical devices and cellular & tissue-based therapy products

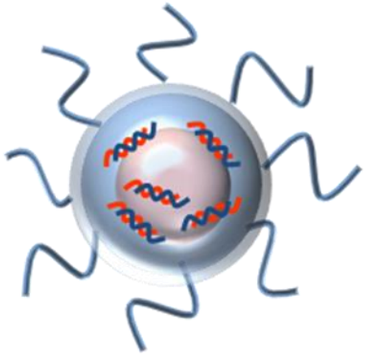
1) Clarification of conditions (confirmation of quality and non-clinical safety) required for the first-in-human study, and development of the evaluation methods
2) Development and standardization of evaluation methods to confirm the usefulness in medical care
3) Clarification of conditions required for approval application, and drafting of guidelines and standards
4) Carrying out official tests, when the problem might happen
5) Global efforts cooperating with foreign regulatory science research organizations

Examples of Regulatory Science for R&D promotion of Cutting-Edge Medical Products

- Division of Drugs: Development and standardization of evaluation methods of cutting-edge pharmaceuticals such as nanomedicines and DDS
- Division of Biological Chemistry & Biologicals: Development and standardization of evaluation methods of antibody drugs and advanced modified protein drugs
- Divisions of Biological Chemistry & Biologicals and Organic Chemistry: Development and standardization of evaluation methods of specialty peptides
- Divisions of Medicinal Safety Science, Molecular Target & Gene Therapy Products, and Biochemistry: Biomarkers for personalized medicine, molecular diagnostics, and radioactive diagnostic agents
- Division of Molecular Target & Gene Therapy: Development and standardization of evaluation methods of oligo-nucleotide drugs
- Division of Molecular Target & Gene Therapy: Development and standardization of evaluation methods of gene therapy drugs
- Division of Cell-based Therapeutic Products: Development and standardization of evaluation methods of tissues and cells for cell-based therapy including iPS cells
- Divisions of Cell-based Therapeutic Products, and Biological Chemistry & Biologicals: Development and standardization of detection, inactivation and removal methods of infectious agents contaminated in raw materials or products
- Division of Medical Devices: Development and standardization of evaluation methods of new biomedical materials including biocompatibility
- Division of Pharmacology : Development and standardization of safety pharmacology tests using iPS cells

The promotion of regulatory science for nanomedicines in Japan

- Research for evaluation of nanomedicines
  - ➢ Development of suitable evaluation methods and standardization



- Drafting technical guidelines
  - ➢ After public consultation, guidelines were issued from the MHLW (Ministry of Health, Labour and Welfare)

1. Joint MHLW/EMA reflection paper on the development of block copolymer micelle medicinal products

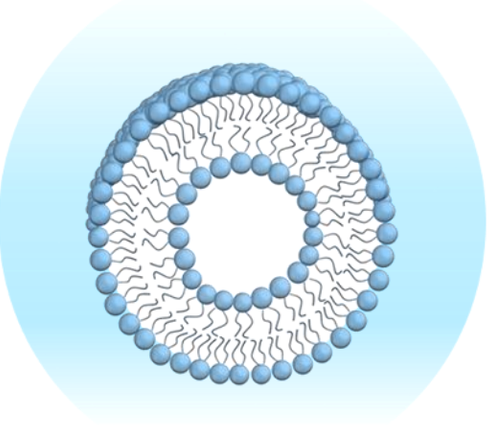
   (January 10, 2014, PFSB/ELS Notification No.011-1)

2. MHLW Guideline for the Development of Liposome Drug Products

   (March 28, 2016, PSEHB/ELD Notification No. 0328-19*)* *New!*

3. MHLW Reflection paper on nucleic acids (siRNA)-loaded nanotechnology-based drug products

   (March 28, 2016, PSEHB/ELD Administrative Notice) *New!*



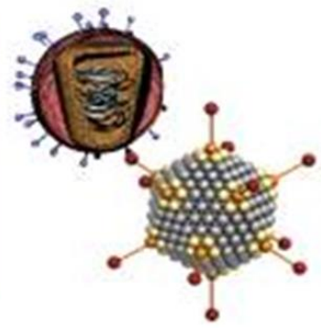
- Exchange of information with international organizations (e.g. International Pharmaceutical Regulators Forum: IPRF)

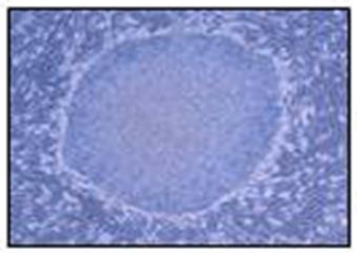
Studies for detection and removal of tumorigenic cells contained in iPS cell-based regenerative medical products

Residual tumorigenic cells/undifferentiated cells in regenerative medical products derived from iPS cells is one of the major concerns in the manufacturing. In this research collaboration among three institutes, we develop *in vivo* tumorigenicity tests using NOG mice and cytotoxic viral vectors to remove undifferentiated cells in products.

Kawasaki City Institute for Public Health

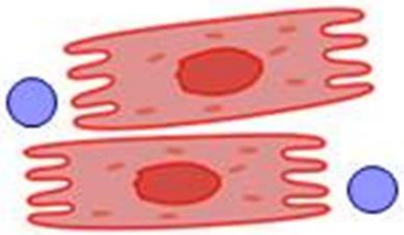
Development of cytotoxic viral vectors specific for undifferentiated iPS cells





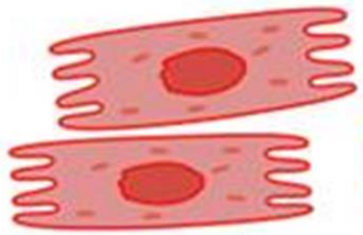
iPS cells

Differentiation



Differentiated cells containing residual undifferentiated cells

Removal



Differentiated cells after removal of residual undifferentiated cells

Transplantation

Quality assessment（identity and impurity）

Non-clinical safety evaluation

NIHS

National Institute of Health Sciences

Preparation of iPS cells and characterization of tumorigenicity tests

Central Institute for Experimental Animals

Rearing NOG mice, transplantation of cells, and monitoring tumor formation

Tumorigenicity tests using NOG mice

国立研究開発法人 日本医療研究開発機構
Japan Agency for Medical Research and Development

New System for Medical R&D

Headquarters for Healthcare Policy (HHP)

- develop a comprehensive plan for the promotion of medical R&D
- integrate medical R&D budget requests of relevant ministries
- make strategic decisions on the allocation of promotional adjustment funds

Advise on Nomination of President and Auditor

Advise on Mid-to-Long Term Targets

Comprehensive adjustment of budget request

Ministries

- Cabinet Secretariat, Office of Healthcare Policy
- Ministry of Education, Culture, Sports, Science and Technology
- Ministry of Health, Labour and Welfare
- Ministry of Economy, Trade and Industry

Handle Nomination and Dismissal of AMED President and Auditor

Present Mid-to-Long Term Targets

Allocate Subsidy Operating Expense

budget concentration

Funding

Japan Agency for Medical Research and Development

Institutes/Researchers

- Provides a unified point of contact for funding and for application procedures.
- Provides support from basic research to practical use.

Examples of the projects awarded in Research on Regulatory Science of Pharmaceuticals and Medical Devices by AMED in F.Y. 2016

Seeds exploration → Quality test (standard, stability) → Non-clinical study → Clinical trial → Approval review → Post-marketing Safety precaution

Studies on safety evaluation and quality control of biopharmaceuticals and oligonucleotide therapeutics

Development and international standardization of drug safety assessment using human iPS cell technology

Study on viral shedding and environment risk assessment of genetically modified viruses used in gene therapy clinical studies

Study on the safety assessment of genome editing technologies for human gene therapy

Studies on the bridging procedure of clinical data obtained by the companion diagnostics

Establishment of frameworks to accelerate international standardization of standards for medical devices

Research on clinical trial guidance for Medical Device

Regulatory science research on therapeutic area standards for the development of drugs in Japan

Establishment of a clinical guideline of endpoints in clinical trials of patients with chronic kidney disease

Utilization of real world evidence using patient registry data to support regulatory decision-making

Research on the efficient clinical trial operations according to GCP

Research on data characterization and outcome validation for promoting pharmaco-epidemiological study utilizing MID-NET for benefit-risk assessments

Analysis of adverse event following immunization and vaccine safety

The study on transfusion guidelines for patients with massive bleeding

Identification of genomic biomarkers and involvement of infection on the onset of severe drug adverse reactions.

Study on how to set an appropriate post-marketing surveillance period for evaluating use outcomes of implantable medical device

Research on regulation of Stand-alone Software as a Medical Device

SUMMARY of the ACTIVITIES

1. MHLW promotes the strategy package (Strategy of SAKIGAKE) facilitating all the process from R&D, clinical research/trials, pre- and post- marketing safety, insurance coverage, through globalization of innovative products which are to be put into practical use, targeting innovative pharmaceuticals which can cure serious illnesses;
2. PMDA is building up the systems, such as priority consultations, prior assessment, and priority reviews in concert with MHLW, takes various approaches such as the introduction of data mining methods and safety evaluation of drugs based on pharmaco-epidemiological methods utilizing electronic medical records, or construction of medical information database network (MID-NET) to enhance and advance safety measures, and has also established the Science Board consisting of external experts to discuss the evaluation methods of innovative drugs;
3. NIHS has carried out RS research to develop the point-to-consider documents or standardized methods for evaluating mainly quality and non-clinical safety of innovative products such as nanomedicines, fully engineered protein drugs, oligonucleotide drugs, or other medical products ; and
4. AMED is supporting about 80 RS research projects by the Grant Program naming “Research on RS of Pharmaceuticals and Medical Devices”.