Regulatory Considerations in Cancer Immunotherapy Product Development Japan Perspective

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and The University of Tokyo

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of PMDA.

Presenter Disclosure Information

<Sumimasa NAGAI>

The following relationships regarding activities in the University of Tokyo only exist:

<Takara Bio Inc, Consulting Fees, Grant to the division which I belong to in the University of Tokyo >

<Sumitomo Dainippon Pharma Co Ltd, Grant to the division which I belong to in the University of Tokyo>

However, these relationships are not related to my presentation.

Agenda

1. Overview

2. New regulation in Japan

3. Recent approvals in Japan

4. Cooperation with academia

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Regulatory Authorities in Japan

PMDA

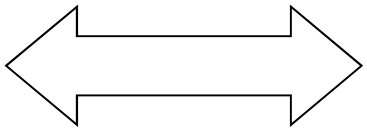
Pharmaceuticals & Medical Devices Agency (PMDA)

- Scientific Review for Drugs & Medical Devices
- GCP, GMP Inspection
- Consultation on Clinical Trials etc.

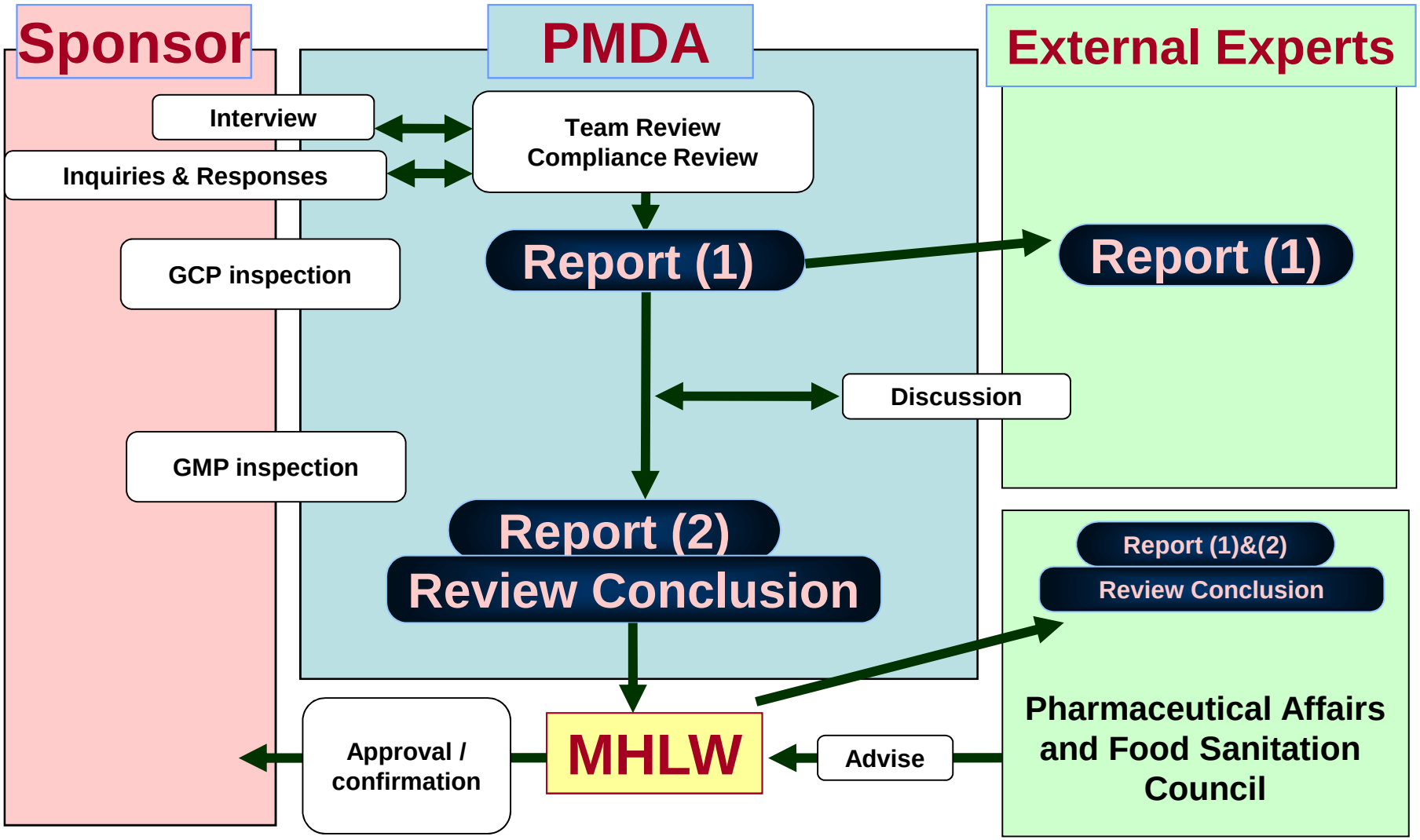
MHLW

Ministry of Health, Labour and Welfare (MHLW)

- Final Authorization of applications
- Publishing Guidelines
- Advisory committee
- Supervising PMDA Activities



NDA Review Process in Japan



New Drug Review Offices of PMDA

New Drug I	Gastroenterology (Gastrointestinal, Liver etc.), Diabetes, Osteoporosis Drugs etc.
New Drug II	Cardiovascular, Anti-Parkinson's & Alzheimer's drugs etc.
New Drug III	Central & Peripheral Nervous System Drugs etc.
New Drug IV	Antibiotics, Anti-Virus, Respiratory Tract Drugs etc.
New Drug V	Oncology Drugs
Office of Cellular and Tissue-based Products	
Office of Vaccines and Blood Products	

Other Related Offices

OTC/Generic Drug		Standards (Pharmacopeia)
Medical Device I	Medical Device II	Medical Device III
Safety I		Safety II
Confirmatory Audit (GLP, GCP, GPSP)		Compliance (GMP/QMS)
Review Management		Review Administration

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New Japanese PMD Act

- MHLW revised the Pharmaceutical Affairs Law (PAL) and implemented the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (PMD act) in November, 2014.

- "Regenerative medical products" were newly defined.

- Conditional and term-limited approval system was introduced only for regenerative medical products because it takes long time to gather sufficient data for assessment of efficacy due to the non-uniform regenerative medical products in terms of quality reflecting the individual differences such as autologous human cell product.

New Japanese PMD Act

In this PMD act, “Regenerative medical products” were newly defined as follows;

- Processed human cells which are used for the purpose of reconstruction/repair/formulation of human body structure/function

- Processed human cells which are used for the purpose of treatment/prevention of disease

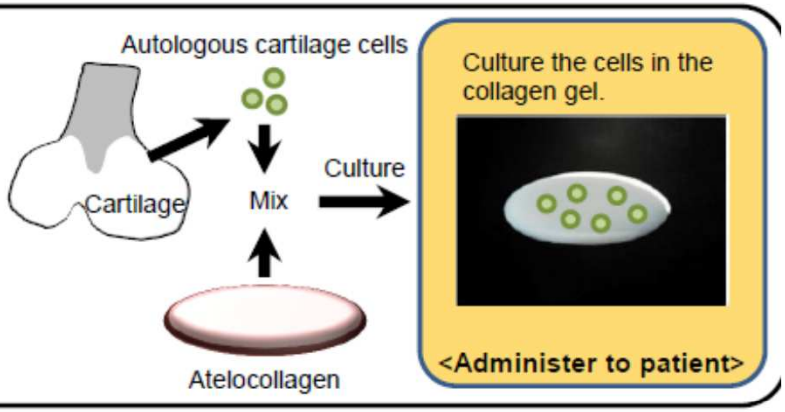
or

- Products which are used by introducing into human cells for the purpose of gene therapy

New Japanese PMD Act

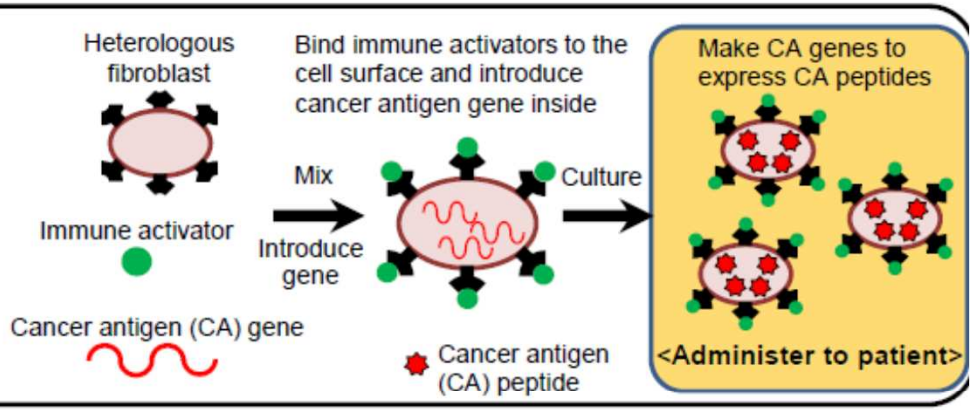
[Example of reconstructing a body structure using cells: Cartilage regeneration product]

Products where autologous cartilage cells are cultured in an *in vitro* collagen gel. Recovery of the cartilage function is anticipated by transplanting the product to the cartilage damaged by injury etc. and producing cartilage-like tissues consisting of cartilage cell – collagen gel etc.



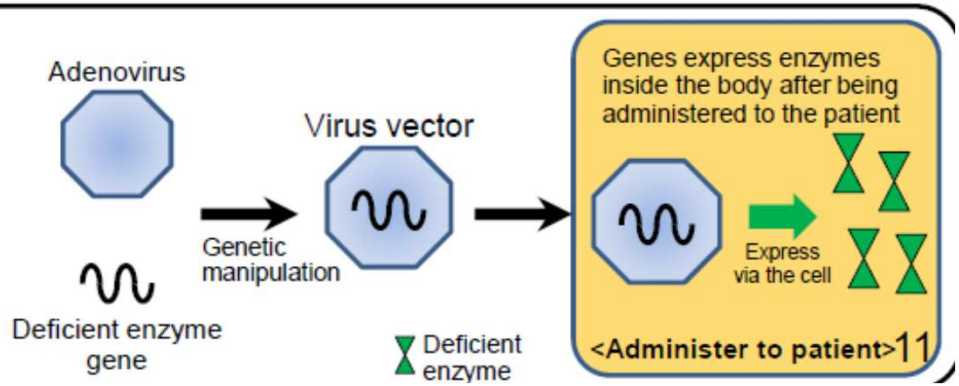
[Example of treating disease using cells: Cancer immunity product]

Therapeutic effects on cancer are anticipated by enhancing the cancer immunity function of the body using cells that contain immunocyte-activating substances and cancer antigen peptides.
* Gene introduction is also carried out for this product.



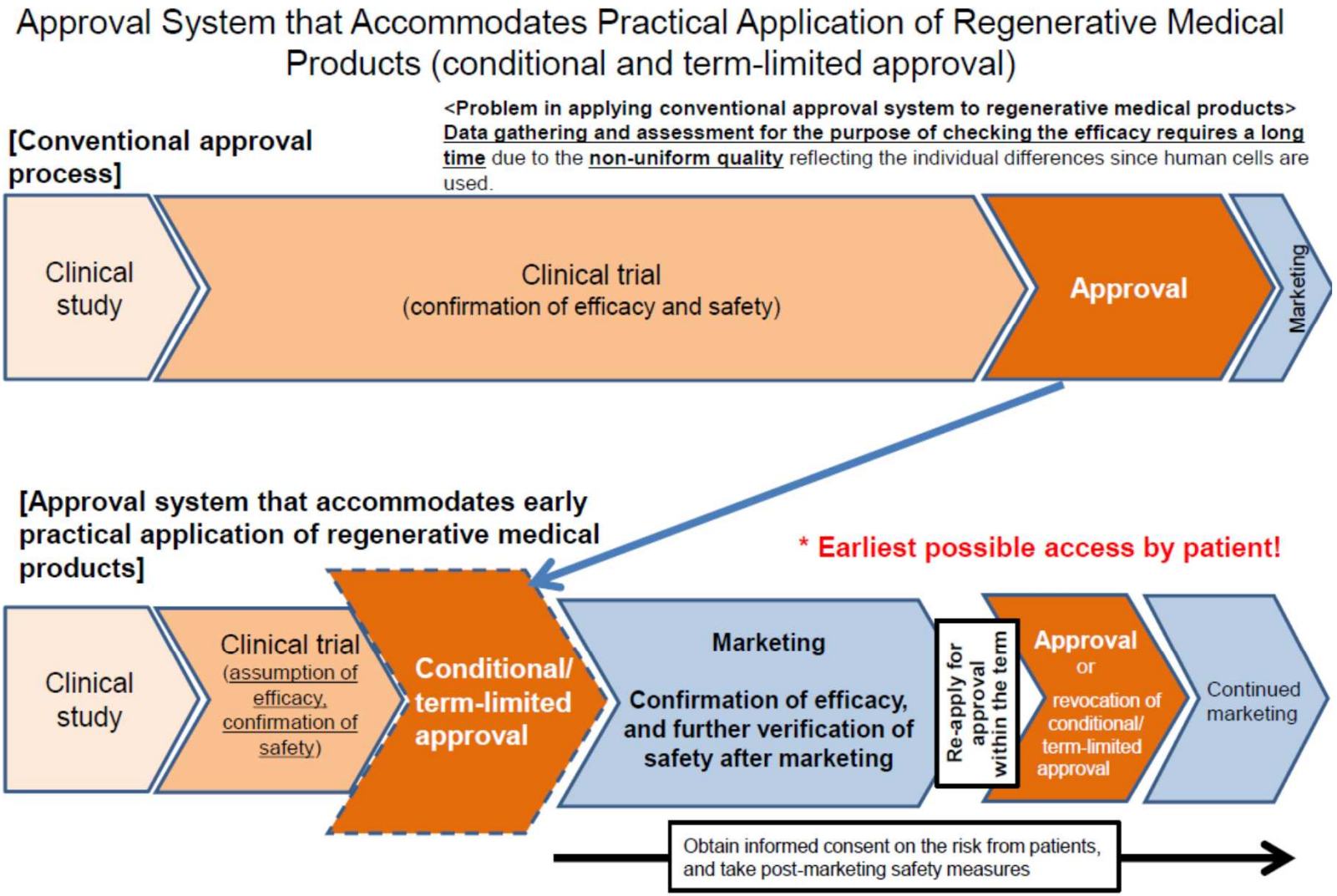
[Example of gene therapy: Hereditary disease treatment product]

Therapeutic effects on hereditary disease are anticipated through administration of viruses retaining congenitally deficient genes (e.g. adenosine deaminase gene) and expression of the introduced genes.



Reference: MHLW HP

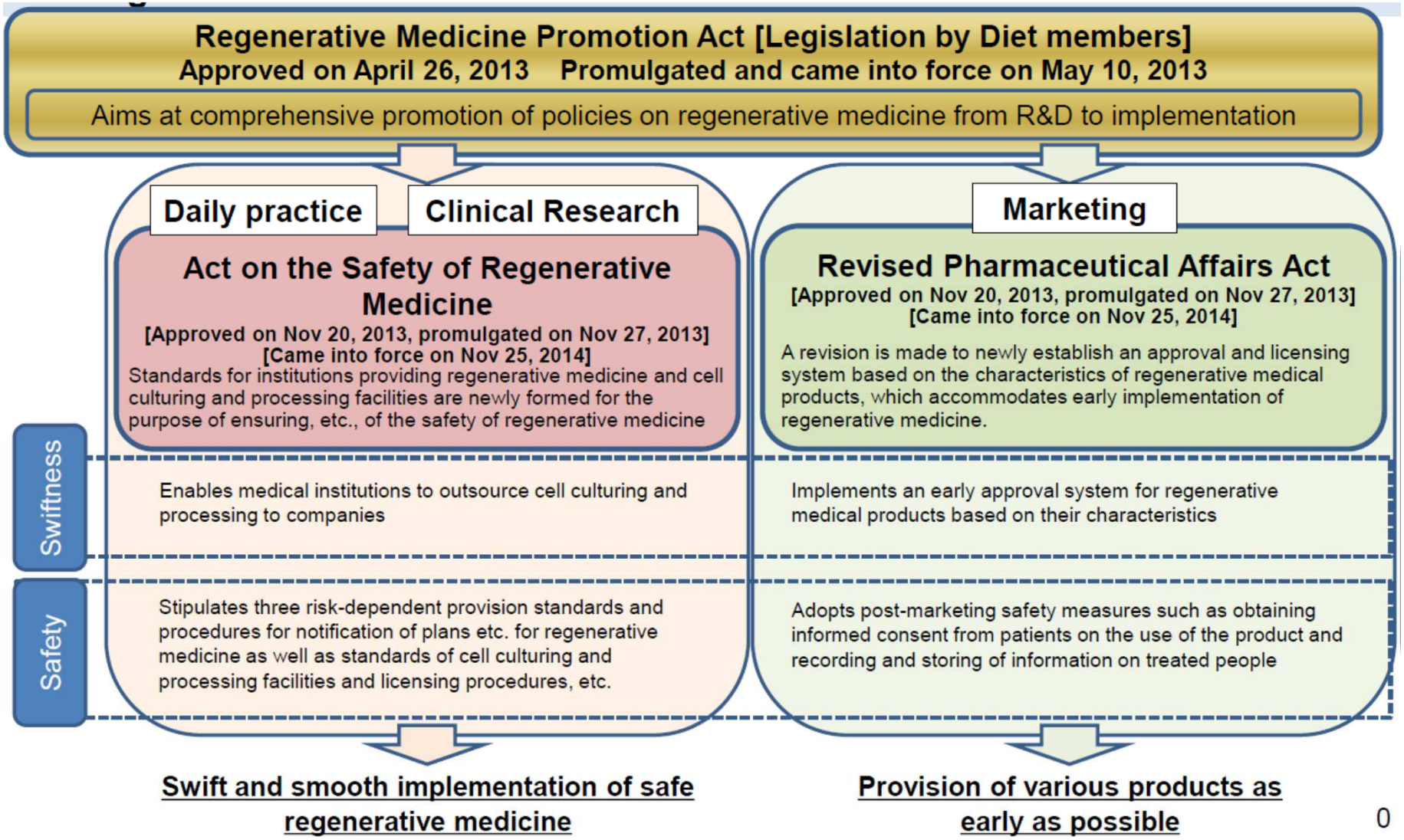
New Japanese PMD Act



- **Efficacy is assumed in a short period of time** compared to the conventional method, from a certain number of limited cases.
- Regarding the safety, side effects etc. in the acute phase can be assessed in a short period of time.

Reference: MHLW HP

Act on the Safety of Regenerative Medicine



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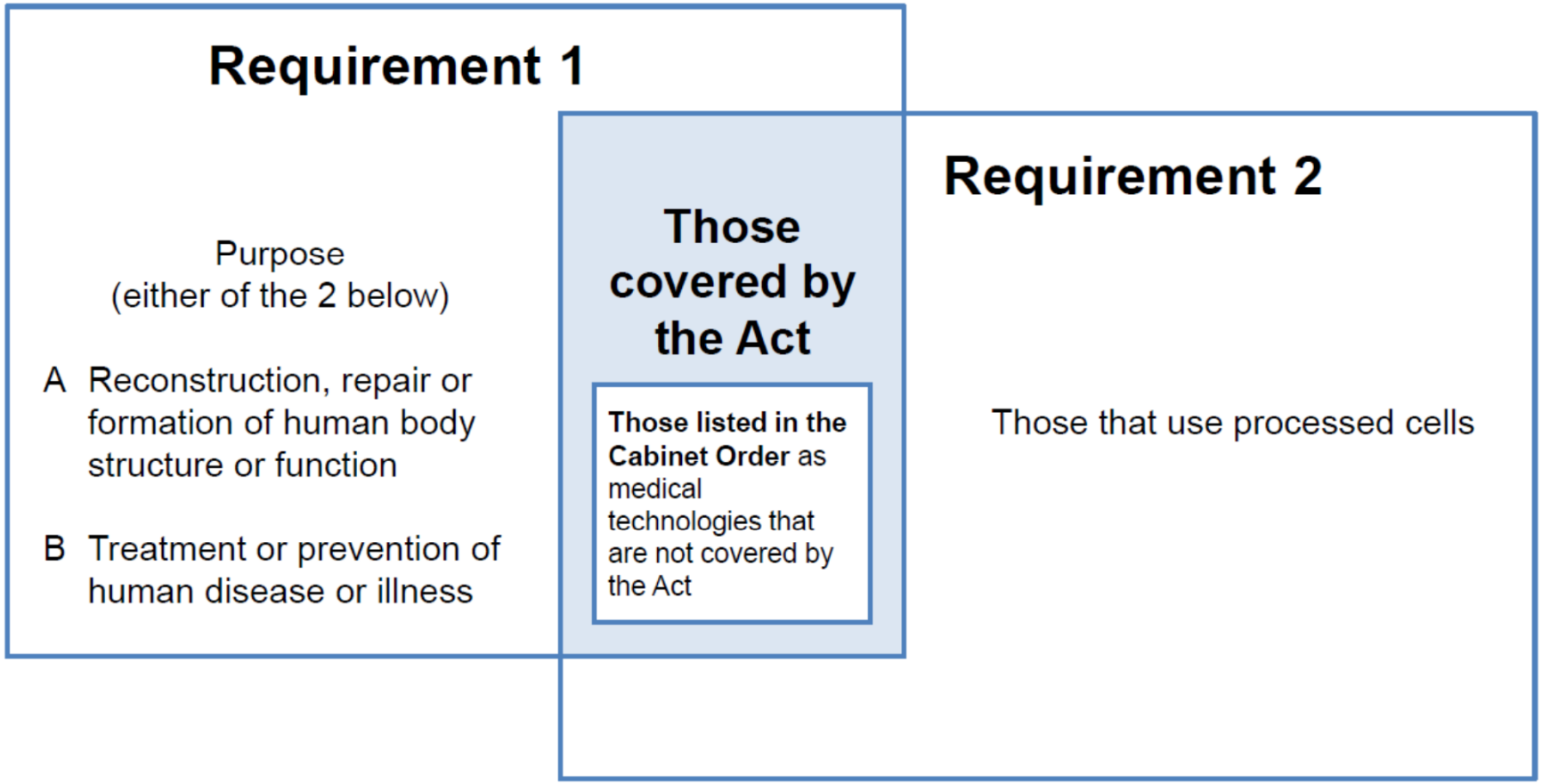


Reference: MHLW HP

Act on the Safety of Regenerative Medicine

Contents of Article 1 (Scope of Regenerative Medical Technology)

Medical technologies **other than the medical technologies** listed below among those that satisfy the requirement of purpose and that use cell products.

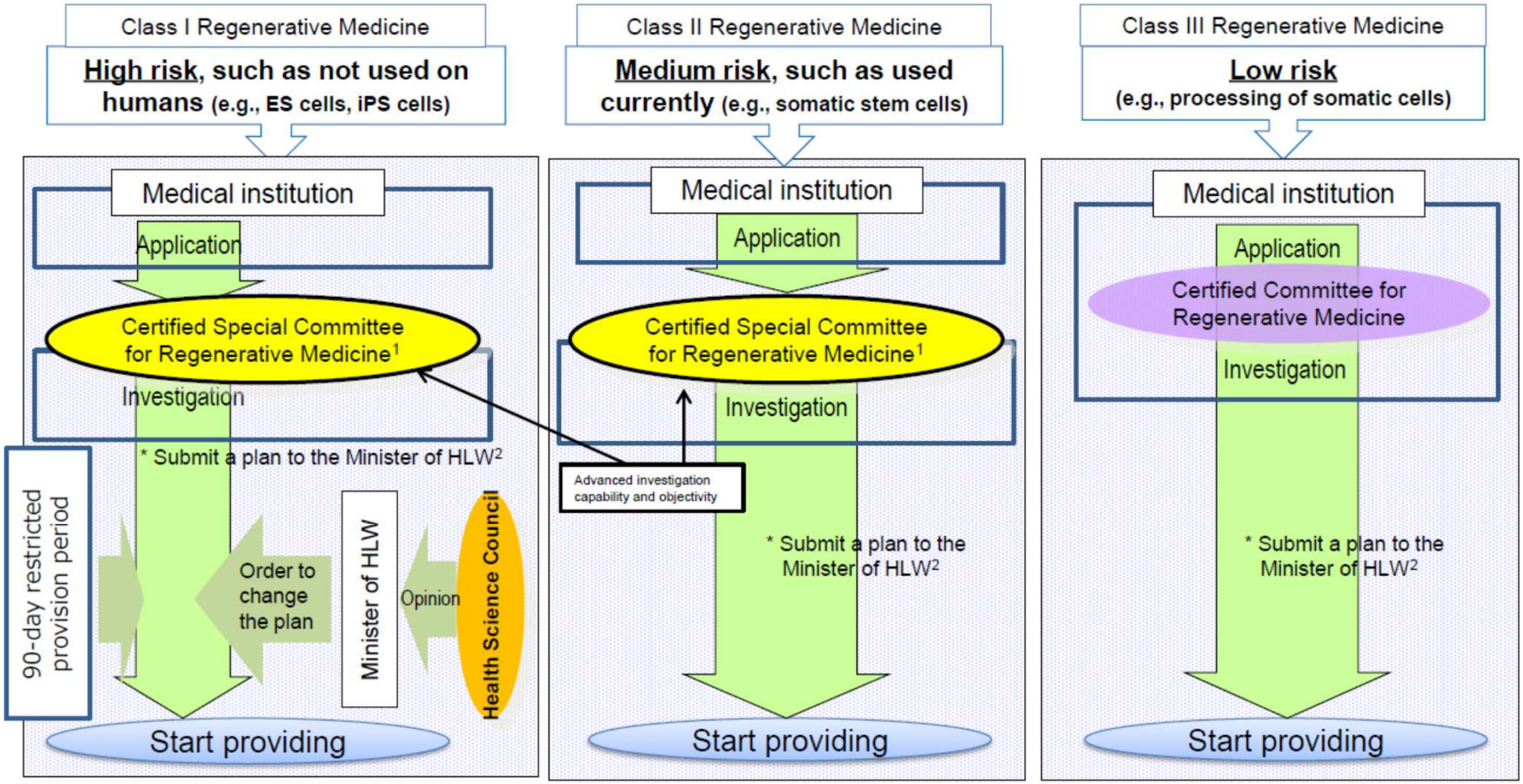
1. Blood transfusion that uses processed cells (excludes those that use gene-transferred blood cell constituents or blood cell constituents manufactured from iPS cells etc.)

2. Hematopoietic stem cell transplantation (excludes those that use gene-transferred hematopoietic stem cells or hematopoietic stem cells manufactured from iPS cells etc.)

3. Assisted reproductive technology: Medical technology that uses processed (e.g., cultured) cells of human sperm or unfertilized eggs (excludes those that use embryotic stem cells established from human sperm or unfertilized eggs collected from humans or processed (e.g., cultured) cells of such embryotic stem cells)

Reference: MHLW HP

Act on the Safety of Regenerative Medicine



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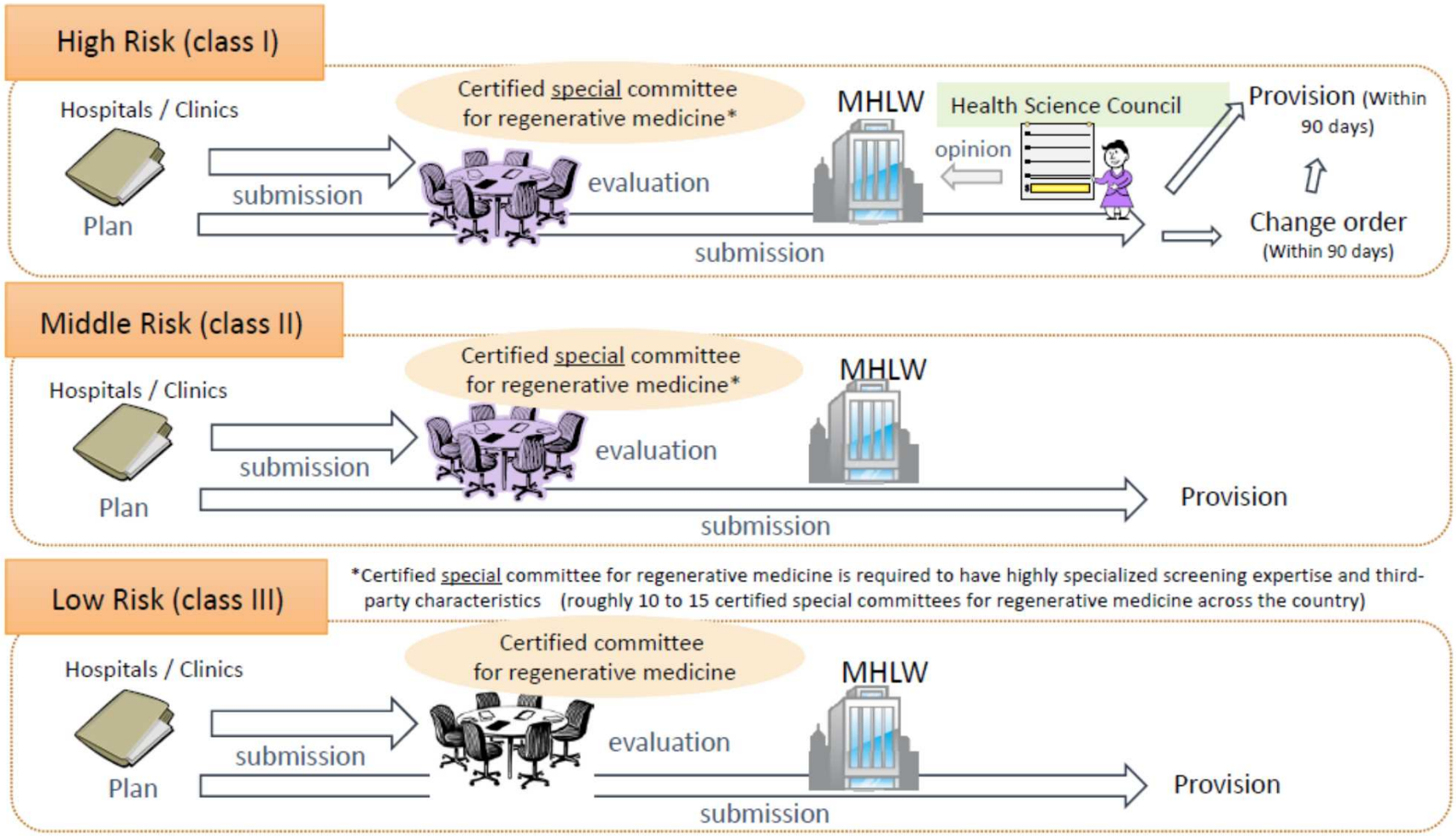


Reference: PMDA HP

SAKIGAKE (Pioneer/Forerunner) Designation

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

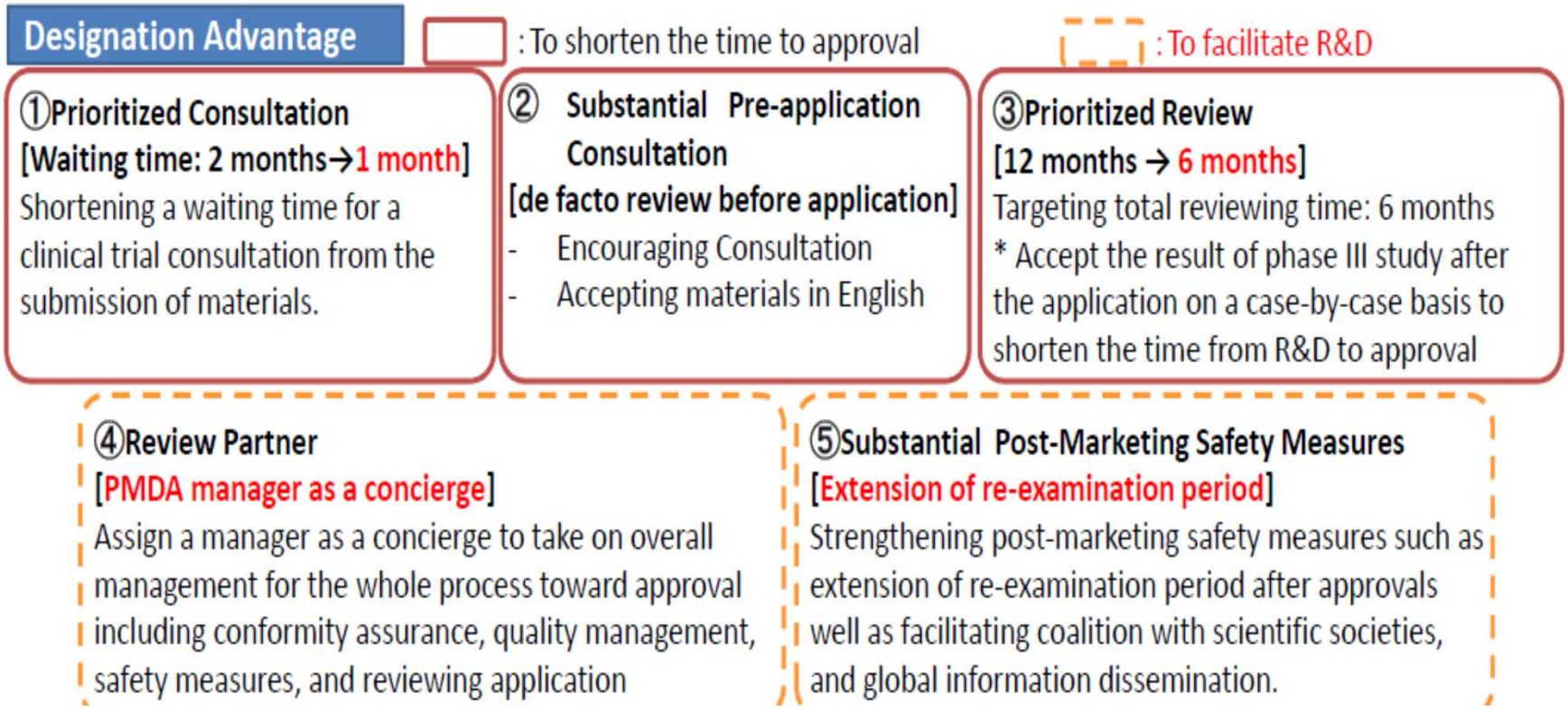
Criteria

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

- Having firstly developed in Japan and planned an application for approvals (desired to have PMDA consultation from the beginning of R&D)

- 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)

SAKIGAKE (Pioneer/Forerunner) Designation



Reference: MHLW HP

Two oncologic products were designated in October, 2015.

- Pembrolizumab for unresectable/advanced/relapsed gastric cancer
- ASP2215 for relapsed/refractory FLT3 mutation-positive AML

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Recent Approvals in Japan

- Cancer Immunotherapy Products

Drug	Indication	Approval Date
Nivolumab (anti-PD-1 antibody)	Unresectable Melanoma	July, 2014
Ipilimumab (anti-CTLA-4 antibody)	Unresectable Melanoma	July, 2015

Recent Approvals in Japan

- Related Oncology Products

Drug	Indication	Approval Date
Mogamulizumab (anti-CCR4 antibody)	Relapsed or refractory CCR4-positive adult T-cell leukemia/lymphoma	March, 2012
	Relapsed or refractory CCR4-positive PTCL/CTCL	March, 2014
	Newly Diagnosed CCR4-positive adult T-cell leukemia/lymphoma	December, 2014

Recent Approvals in Japan

- Related Regenerative Medicine Products

Drug	Indication	Approval Date
Human Mesenchymal Stem Cell-Based Product	Acute GVHD	September, 2015 (Regular Approval)
Autologous Skeletal Myoblast Sheet-Based Product	Severe Ischemic Heart Failure	September, 2015 (Conditional and Term-Limited Approval)

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Pharmaceutical Affairs Consultation on R&D Strategy

- In order to achieve realization of innovative drugs, medical devices, and cellular and tissue-based products originating from Japan

- PMDA launched the Pharmaceutical Affairs Consultation on R&D Strategy in July 2011 with lower fee than normal consultation with companies

- Mainly for universities, research institutions, and venture companies that possess promising “seed-stage” research or technologies (especially, translational research regarding cancer immunotherapy is active in academia)

Project for Enhanced Practical Application

- In 2012, MHLW started “Project for Enhanced Practical Application of Innovative Drugs, Medical Devices and Regenerative Medical Products”

- In order to promote personnel exchange and cooperation in writing guidelines on evaluation of innovative medical products between the PMDA and academia

- Two projects related to cancer immunotherapy are ongoing.

  1. Mie University

     Non-clinical and clinical evaluation of cancer immunotherapy

  2. Institute of Medical Science, University of Tokyo

     Non-clinical and clinical evaluation of oncolytic virus therapy

Project in Cooperation with Mie University

- The guidance on early-phase clinical studies of cancer immunotherapy was published.

- The following documents are now being prepared.

  Guidance on late-phase clinical studies of cancer immunotherapy

  Guidance on combination cancer immunotherapies

  Guidance on non-clinical aspects of adjuvants of cancer vaccines

  Guidance on CMC and non-clinical aspects of cancer cell therapy

Project in Cooperation with Mie University

2015 Guidance on

Cancer Immunotherapy Development

Early-Phase Clinical Studies

- For Development of Safe and Effective Immunotherapy -

Published on January 30, 2015

Publicly available in the PMDA website
http://www.pmda.go.jp/files/000206319.pdf

Guidance on Early-phase Clinical Studies

Dose

- MTD may not be identified for cancer vaccination because DLT rarely occurs within the dose range studied. In addition to a method of determining a recommended dose based on toxic reactions, direct use of immune responses and other responses will be considered in finding the dose.

Assessment Period

- Caution should be exercised when selecting the assessment period as some cancer immunotherapies may cause late-onset toxicity or produce delayed responses.

Challenges

Endpoint

- Despite the lack of tumor shrinkage, some cancer immunotherapies have the potential to slow progression or improve survival.

→How do we find promising cancer immunotherapy in early-phase clinical studies when response rate is low?

- The onset of effect may be delayed because of the mechanism of action specific to cancer immunotherapy. Considering an onset pattern of effect, immune-related response criteria (irRC) are proposed as criteria for tumor regression.

→Are irRC and/or other new criteria really necessary for cancer immunotherapy?

Cancer Peptide Vaccines

Cancer Science

Japanese Cancer Association JCA

Open Access

Report

Guidance for peptide vaccines for the treatment of cancer

Yoshiyuki Yamaguchi,[1] Hiroki Yamaue,[2] Takuji Okusaka,[3] Kiyotaka Okuno,[4] Hiroyuki Suzuki,[5] Tomoaki Fujioka,[6] Atsushi Otsu,[7] Yasuo Ohashi,[8] Rumiko Shimazawa,[9] Kazuto Nishio,[10] Junji Furuse,[11] Hironobu Minami,[12] Takuya Tsunoda,[13] Yuzo Hayashi,[14] and Yusuke Nakamura,[15] The Committee of Guidance for Peptide Vaccines for the Treatment of Cancer, The Japanese Society for Biological Therapy

Cancer Sci **105** (2014) 924–931

Challenges

Combination therapy

- There is a high hope for combination cancer immunotherapy which combines therapies with different modes of action.

Ex.) checkpoint inhibitor + cancer vaccine
cancer immunotherapy + chemotherapy
cancer immunotherapy + radiation

→ What is the most appropriate clinical trial design for these combination therapies?

Lessons and Take Home Messages

- The PMD act was implemented in November, 2014.
- “Regenerative medical products” were newly defined.
- Conditional and term-limited approval system was introduced only for regenerative medical products.

- In the project for enhanced practical application in cooperation with academia, some guidance documents related to cancer immunotherapy are published or being prepared.