Pharmaceuticals and Medical Devices Agency

Regulatory Reform for Regenerative Medicine in Japan

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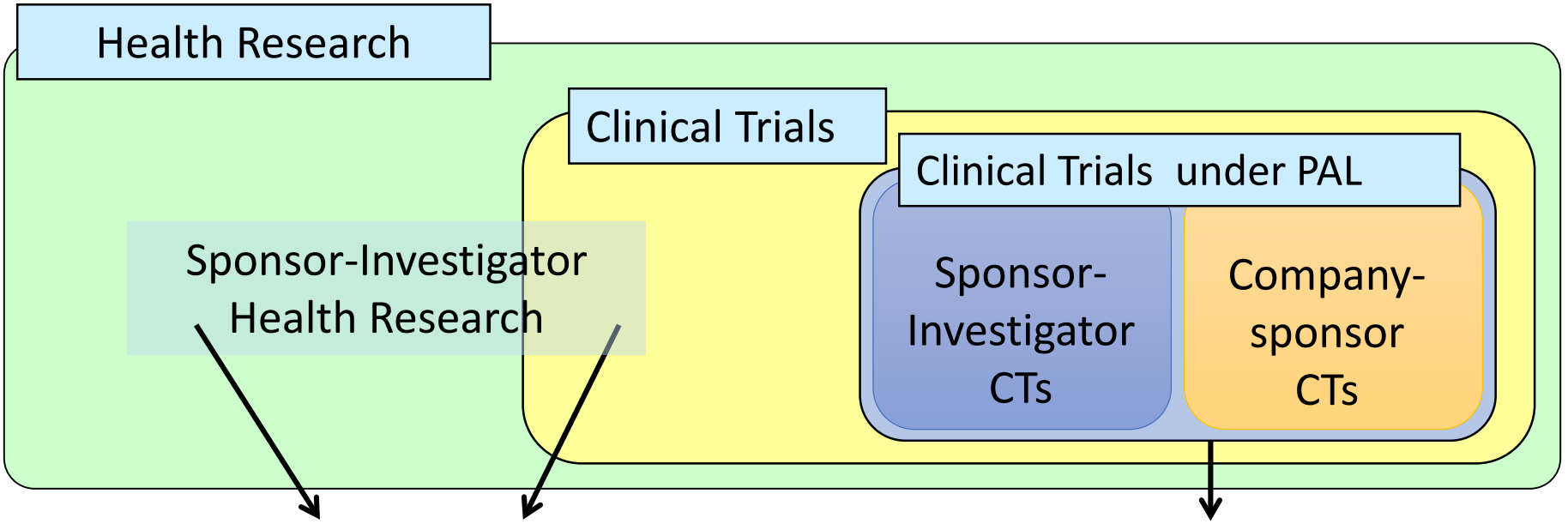
The contents of this presentation represent the view of this presenter only, and do not represent the views and/or policies of the PMDA

Current Health research regulations in Japan



Academic Purpose (other than MA)

- Observational studies
- Interventional studies
- Human Genome Analysis

Covered by MHLW itself

Product Marketing Authorization Purpose

Interventional studies intended for application for MA of drugs and medical devices under Pharmaceutical Affairs Law (PAL)

Covered by PMDA

Regenerative medicine & cell therapy in Japan

Clinical trials using human stem cells (non-PAL) Academic purpose
(under the Guideline for Human Stem Cell Clinical Trials)

90 clinical trials have been approved as of February 2014

Cancer immunotherapy

Six types of therapy are currently provided in approved university hospitals as “advanced care”
* Partially covered by national health insurance

No statistics available for those provided outside of national health insurance scheme

Regenerative medical products (under Pharmaceutical Affairs Law)

Number of marketed products : 2

(JACE (autologous cultured epidermis), JACC (autologous cultured cartilage))

Number of clinical trials initiated : 11 (including 2 gene therapy products)

As of May 2014

Stem Cell Clinical Trials Approved in Japan (non-PAL)

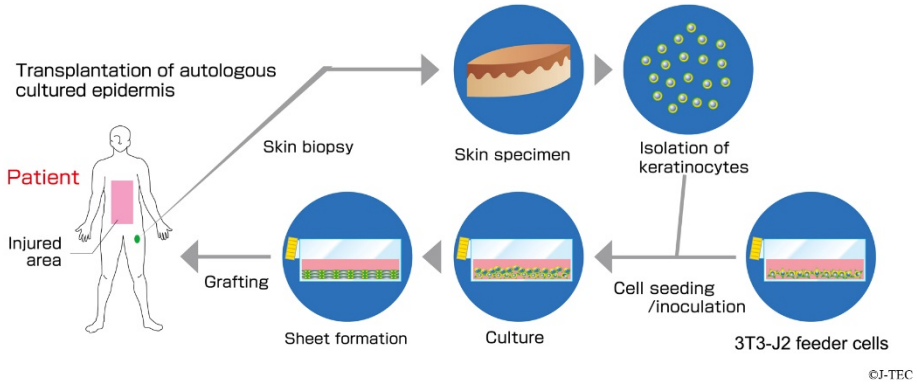
Source	Origin	No. of Institution
Adipose Tissue	autologous	10
Bone Marrow	autologous	27
Bone Marrow	allogeneic	2
Cord Blood	autologous	1
Corneal Epithelium	autologous	1
Corneal Endothelium	allogeneic	1
Corneal Tissue	allogeneic	2
Dental Tissue	autologous	3
Myocardium	autologous	3
Nasal Epithelium	autologous	1
Oral Mucosa	autologous	9
Periosteum or Chondrocyte	autologous	2
Peripheral Blood	autologous	20
Skeletal Muscle	autologous	3
Synovial Tissue	autologous	4
IPS Cells	autologous	2

As of April 2014, MHLW

Two authorized products under PAL

Ref. Japan Tissue Engineering Co., Ltd. (J-TEC), HP

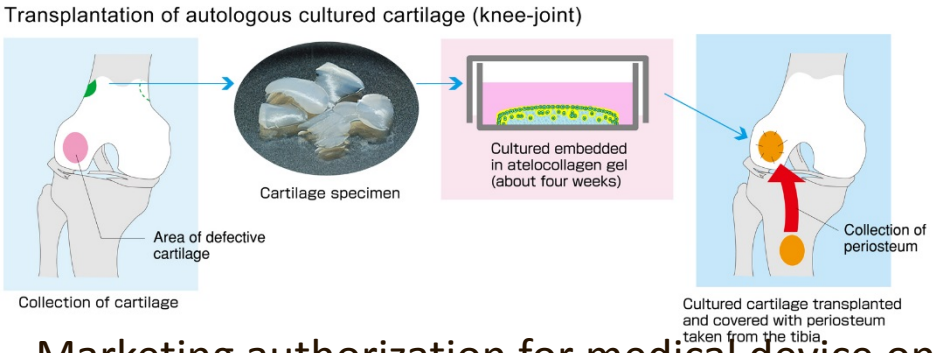
Autologous Culture Epidermis ***JACE***



Indication: serious burns treatment (limited to the burns of more than 30% of the body surface area)

Marketing authorization for medical device on 29 October 2007 (submission: 6 October 2004)

Autologous Cultured Cartilage ***JACC***

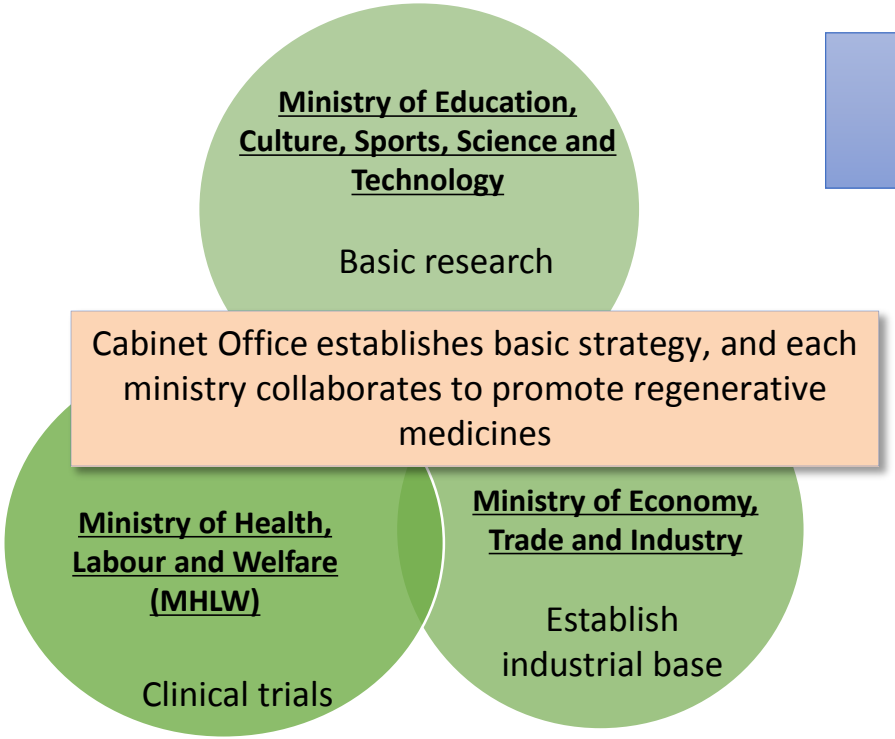


Indication:
Relief of symptoms of traumatic cartilage defects and osteochondritis dissecans (exclude osteoarthritis) for knee joints. (limited to a defect area of over 4cm2 with no alternative therapy.)

Marketing authorization for medical device on 27 July 2012 (submissic
24 August 2009)

Government policy

- Integrated support from basic to clinical research
- Development of infrastructure to promote regenerative medicines
- Support utilizing iPS cells as a drug-discovery tool



Regenerative Medicine Promotion Act
(Enacted in May 2013)

Goals for the next 7 years

- Apply new drugs developed by iPS cells technology in clinical trials
- Increase the number of approved cellular therapeutic products
- Expand the target of illness in clinical trials
- Develop equipment or devices related to regenerative medicines

New legislative Framework

These two acts were promulgated in November 2013 by the Japanese Diet (Parliament) in line with the **Regenerative Medicine Promotion Act**, in order to reform the pharmaceutical and medical regulation related to regenerative medicine

- Revision of the Pharmaceutical Affaires Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD. Act)

- The Act on the Safety of Regenerative Medicine

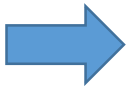
These two acts are scheduled to be enacted on 25 November 2014

Other related governmental policy:

- **Healthcare and Medical Strategy Promotion Act (2014.5)**
- **Japan Medical Research Development Institution Act (2014.5)**

Background for new legislations

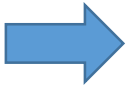
1. Needing legal basis for the guideline to secure safety of stem cell therapies
2. Growing need for collaboration between medical institutions and industry from the early stage of development



New legislation is needed for prompt and safe regenerative medicine.

→ Act on the Safety of Regenerative Medicine

3. The existing framework in Pharmaceutical Affairs Law does not fit for the characteristics of regenerative and cellular therapeutic products



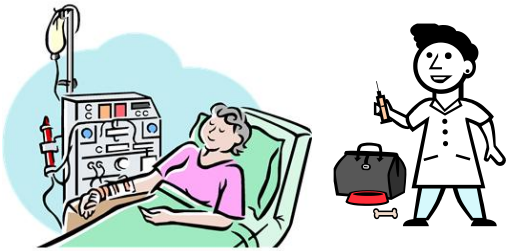
Definition of regenerative and cellular therapeutic products and establishment of new framework are needed

→ Revised Pharmaceutical Affairs Law (name change to PMD. Act)

Two Acts regulating regenerative medicine & cell therapy

Regenerative Medicine

All medical **technologies** using processed cells which safety and efficacy have not yet been established



The Act on the Safety of Regenerative Medicine

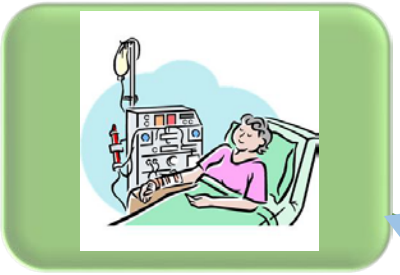
It may be similar to researcher initiated IND application system

Production and marketing of regenerative and cellular therapeutic **products** by firms

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

* Two laws will be enacted on 25 November 2014

Overview of the Act on the Safety of Regenerative Medicine



Provision of regenerative medicine

I. Obligate hospitals and clinics to submit plans

Hospitals / Clinics

II. Enable commissioning cell processing to licensed enterprises

Cell processing

Certified committee for regenerative medicine

Certification

Cell processors

III. Obligate CPCs to notify or obtain licence

Notification (Hospitals / Clinics) or Application for a license (Firms)

Minister of Health

Manufacturing business License or notification

- Hospital in-house CPC (Cell Processing Center)
  - ✓Notification of facility and equipment

- CPC outside hospital

  If physician commission cell processing to a CPC outside hospital, license or accreditation by MHLW is required
  - ✓Manufacturing Business License for Local manufacturing site)
  - ✓Manufacturing Business Accreditation for Foreign manufacturing site

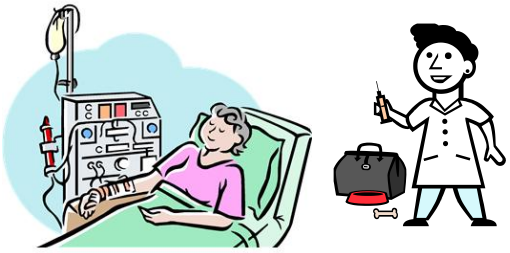
License/accreditation is subject to PMDA's site inspection and compatible to business license/accreditation of PMD Act.

GCTP (Good gene, Cell and Tissue Practice) (≈ Good Tissue Practice + GMP/QMS) will be applicable to both types of CPCs

Two acts regulating regenerative medicine & cell therapy

Regenerative Medicine

All medical technologies using processed cells which safety and efficacy have not yet been established



The Act on the Safety of Regenerative Medicine

Production and marketing of regenerative and cellular therapeutic products by firms

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

* Two laws will be enacted in November 2014

Company driven IND and product approval system

Revision of Pharmaceutical Affairs Law

- **Revisions of Drugs and Medical Devices Articles**
  - Relevant party's obligations are specified to ensure quality, safety, and efficacy of drugs and medical devices.
  - MAH's obligation to notify labeling and its revision, reflecting the latest findings
- **Revisions of Medical Devices Articles**
  - Independent Chapter for "Medical Devices"
  - Expansion of Third party certification system to higher risk devices
  - Quality Management System (QMS) adherent to ISO 13485
  - Other revisions related to medical devices
- **Additions for Regenerative Medical Products**
  - Definition and independent chapter for Regenerative Medical Products
  - Introduction of conditional/time limited approval system

Definition of “Regenerative Medical Products” in Japanese Legislation

- **Regenerative medical products** are defined as processed human cells that are intended to be used 1) for either (1) the reconstruction,repair, or formation of structures or functions of the human body or (2) the treatment or prevention of human diseases,or 2) for gene therapy.

Under the Revised PAL (=Pharmaceuticals and Medical Devices Act. (PMD Act.))

Cellular and Tissue based Products and Gene therapy Products

Advanced-therapy medicinal products (ATMPs)

Regulation (EC) No 1394/2007

Early Access schemes of ICH 3 parties

US	EU	JAPAN
Priority Review		Priority review
Accelerated approval for serious or life-threatening illnesses	Conditional MA MA under exceptional circumstances	Conditional Approval for Oncology drug, Orphan drug Conditional & Time-limited approval for regenerative medicine
Break through therapy & Fast Track designation		Forerunner Review Assignment

Various agencies have various approaches to accommodate patient access though they have certain similarity.

The Pharmaceuticals and Medical Devices Act (PMD Act)

◆ Separate category and definition of “regenerative medical products”

Difficult to gather and evaluate the data for efficacy of regenerative medical products in a short time due to heterogeneity of cells

➡ To secure timely provision of safe regenerative medicines, a new regulatory framework is needed

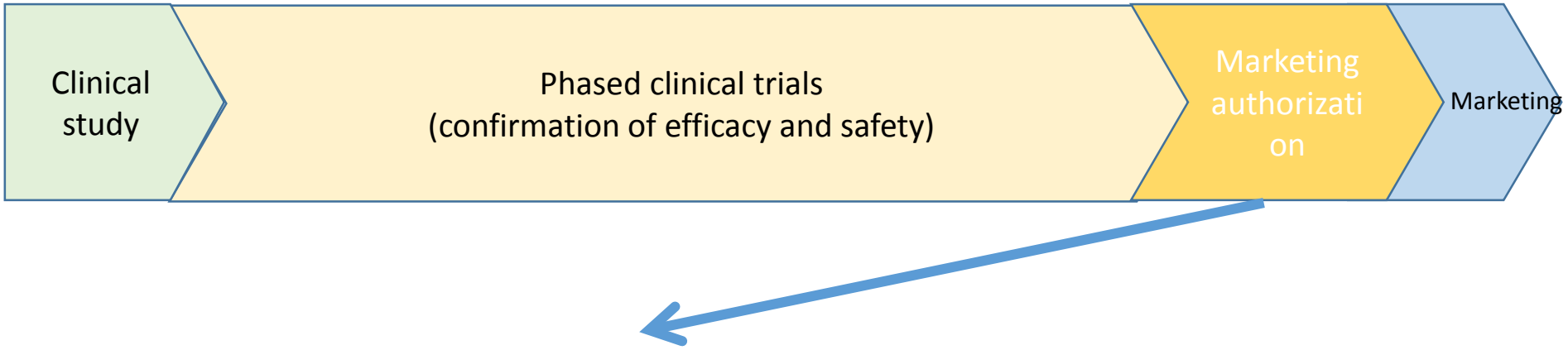
Expedited approval system for regenerative medical products

After the safety is confirmed and the results predict likely efficacy, the product will be given conditional, time-limited marketing authorization in order to enable timely provision of the products to patients.

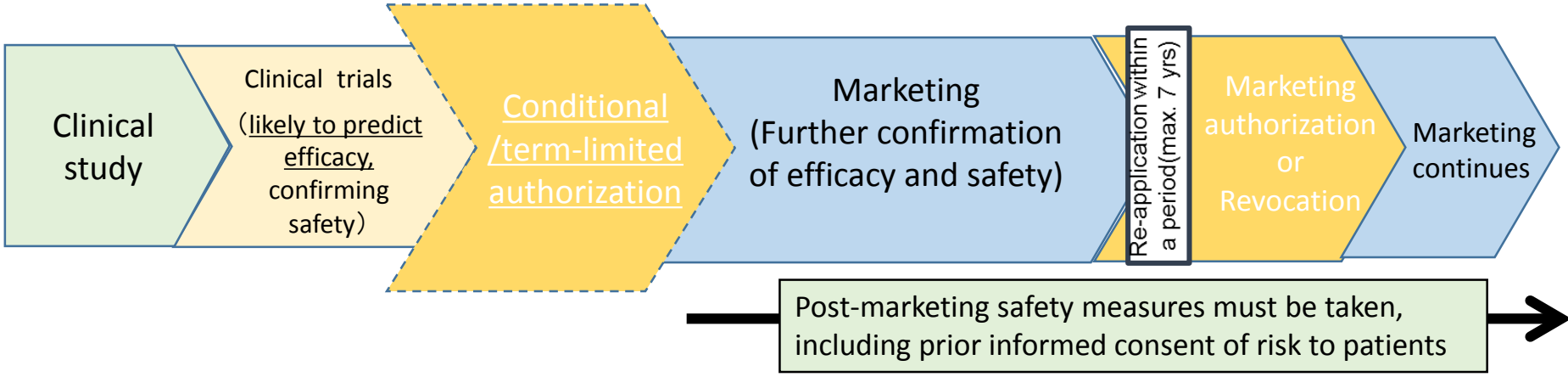
Expedited approval system under PMD Act

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

[Traditional approval process]

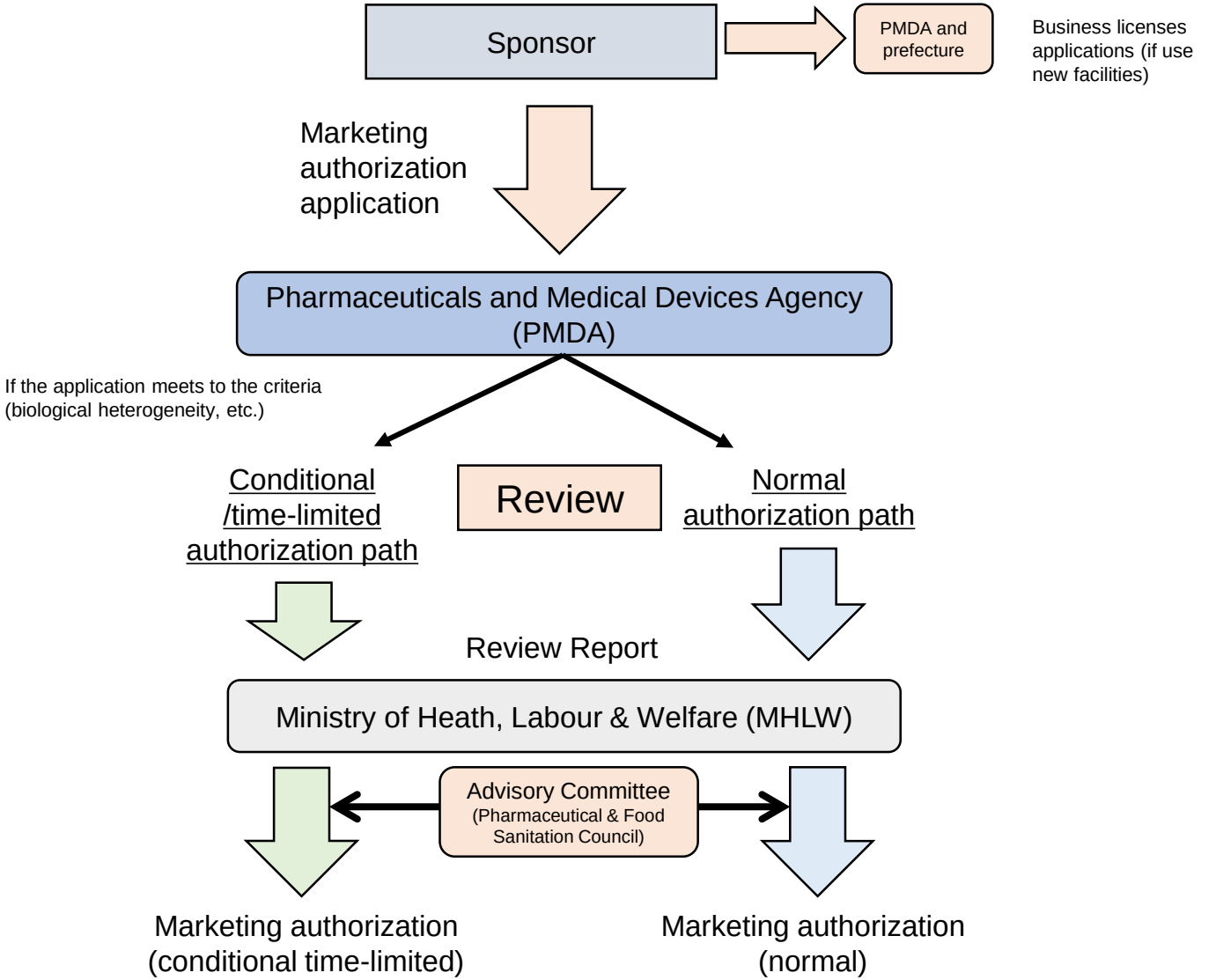


[New scheme for regenerative medical products]



Review Pathway of regenerative medical products

Application and review flow of regenerative medical product under the PMD Act. (revised PAL)



Ref. Hara A. Sato D. Sahara Y. New Governmental Regulatory System for Stem Cell–Based Therapies in Japan. *Therapeutic Innovation & Regulatory Science*. 2014; DOI: 10.1177/2168479014526877

Likely to predict efficacy (clinical benefit)

- To approve products based on the limited data, such as surrogate endpoints in exploratory study.
- Similarity to **accelerated approval of** USFDA * The product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (ref.)
- We have experiences in the orphan drug area.

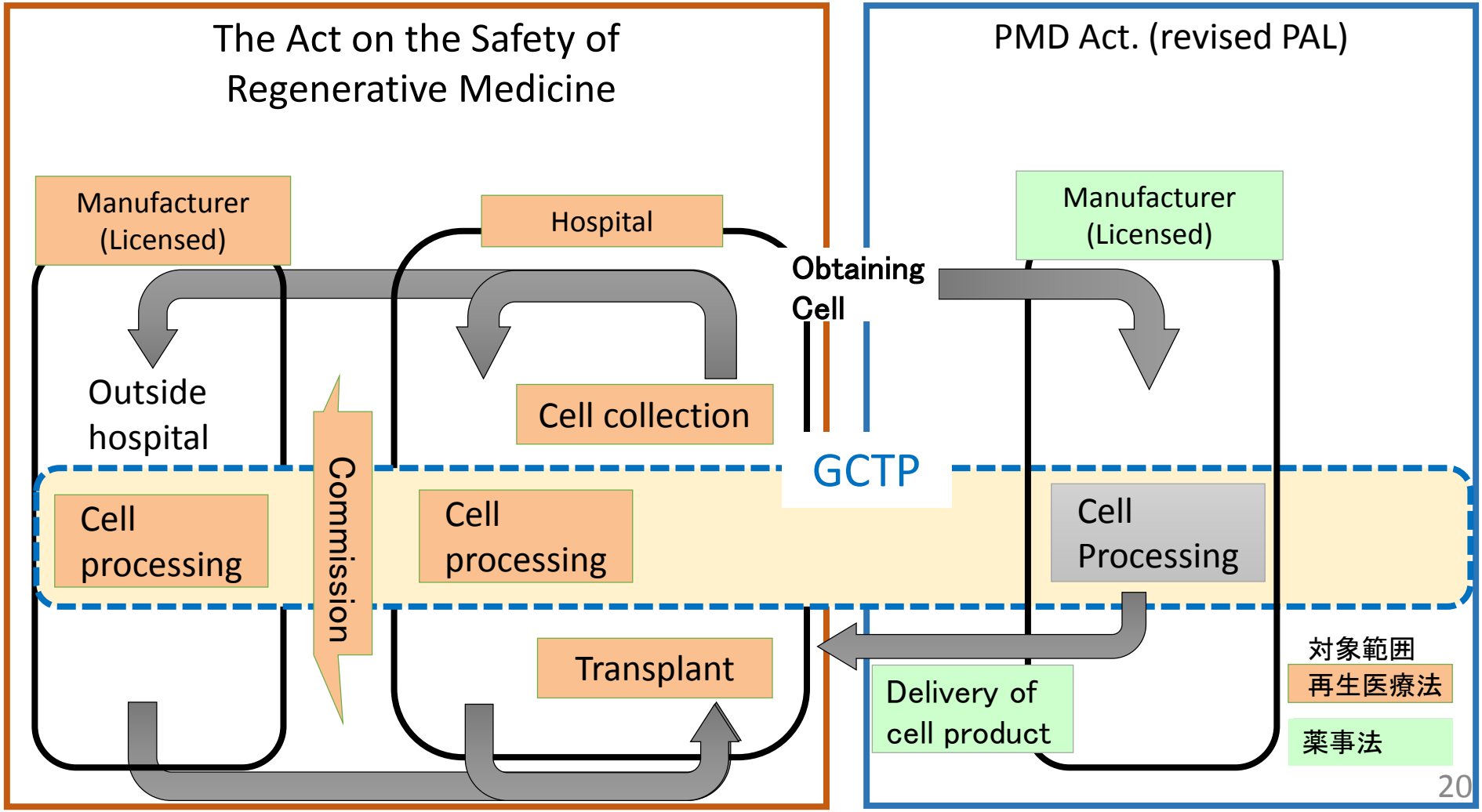
Ref.) USFDA--Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (57 FR 58958, Dec. 11, 1992)

- It applies to certain new drug products in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.
- Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
- The drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity..
- Approval will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit (such as OS).
- Postmarketing studies would usually be studies already underway.
- FDA may withdraw approval, if a postmarketing clinical study fails to verify clinical benefit; ……

Consistent parts of the two Acts

Medical technologies using processed cells
(except clinical trials under PMD Act.)

Regenerative Medical Products



GCTP (Good gene, Cell & Tissue Practice)

Quality System Requirement for regenerative medical technologies / products, considering the characters of these products; such as raw materials that cannot be sterilized

- Quality Risk Management
- Manufacturing Control (Sterility assurance, Prevention of Cross-contamination..)
- Quality control (Verification / validation, Quality review)
- Facility requirement

Guidance notification was released on 9 October 2014

It is necessary to consider whether the risk is manageable,
- not only from the facility point of view,
- but from the effects of the manufacturing operation, such as the evaluation of performance.

Public no-fault Indemnity system for patient injuries associated with products approved under PMD Act.

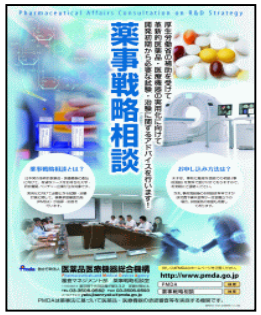
	Biological device	Regenerative medical products
Conditional and time limited approval	NA	√
Adverse Drug Reaction Relief Fund	NA	√
Infection Relief Fund	√	√

Private Insurance products will be available for clinical studies under the Act on the Safety of Regenerative Medicine

Pharmaceutical Affairs Consultation on R&D Strategy

Valley of Death

-Shortage of funds, Knowledge on Regulation and developmental strategy



Basic Research

Pharmaceuticals and Medical Devices candidates

Strategic Consultation

- Quality Study
- Non-Clinical Study
- Clinical Trial (Up to POC studies)

Practical Use

Innovative Products

* Further studies are handled by the Regular Consultation

Consultation on quality and battery of pre-clinical, including examining tumorigenicity, biological ingredient safety

Consultation on endpoints or sample size of early clinical trial

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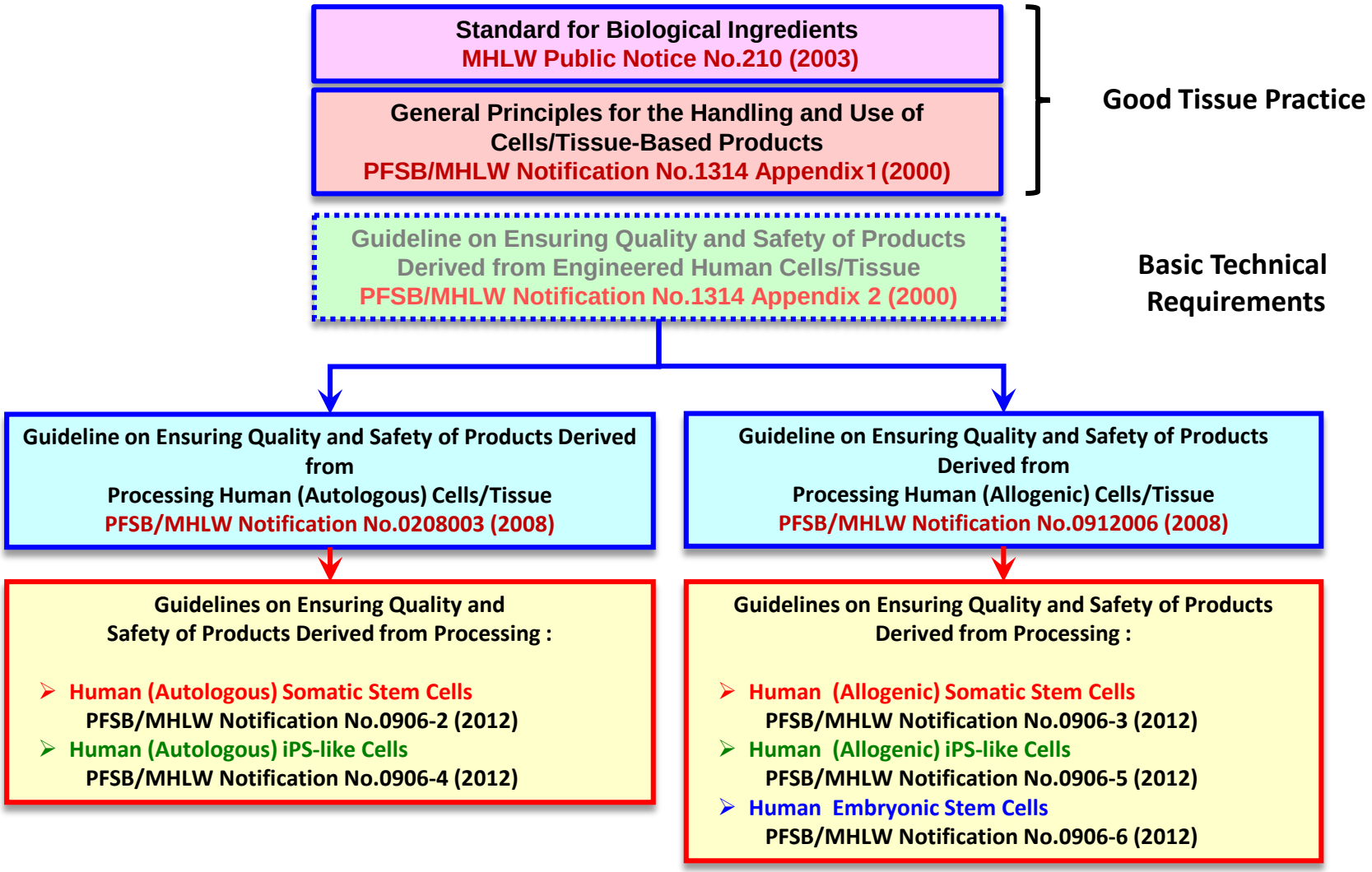
Flow of Strategy Consultation

Introductory Consultation (684) → Pre-Consultation (813) → Face-to-Face Consultation (209)

(7/1/2011 – 6/30/2014)

System of general guidelines for quality and safety(pre-clinical) for Human Cell & Tissue-Based Products since 2000.



Related Specific Guidelines for Products Evaluation

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue

- Autologous (2008)
- Allogeneic (2008)

Guidelines on Ensuring the Quality and Safety of Products Derived from Processed Human Stem

- Autologous Somatic Stem Cells (2012)
- Autologous iPS-like Cells (2012)
- Allogeneic Somatic Stem Cells (2012)
- Allogeneic iPS-like Cells (2012)
- Embryonic Stem Cells (2012)

Points to Considers for the Evaluation of Specific Products

・Cell sheet for heart failure (2010) ・Corneal epithelial cell sheet (2010) ・Corneal endothelial cell sheet (2010)
・Articular cartilage repair (2010) ・Cell sheet for periodontal tissue regeneration (2011)
・Autologous induced pluripotent stem cells-derived retinal pigment epithelial cells (2013)
・Allogeneic induced pluripotent stem cells-derived retinal pigment epithelial cells (2014)

The Science Board Report. PMDA.

・ Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs)* and iPSCs as Their Starting Materials (2013)

Establishment of Science Board

Basic Research

Seeds of new drug / medical devices

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

Practical use

Innovative medical products

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 Review Innovation

Establishment of the 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 such as basic research, development support, product review, and post market safety measures.

Board members

Academia (Knowledge of the Latest Innovative Technologies)

Outcome of the Science Board

Cellular & Tissue-based Products

- Current Perspective on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from iPSCs and iPSCs as Their Starting Materials (Aug. 21, 2013)

Pharmaceuticals, Biologics

- Summary of Discussion on Non-clinical Pharmacology Studies of Anticancer Drugs (Dec. 10, 2013)

- Summary of the discussion on assessment of the current status of personalized medicine relating to drug development and review (Mar. 11, 2014)

The Science board outcome is to be contributed to resolve questions expected in the scientific consultation during development.

The Science board discussion, further

- Further to the discussion in the last term, in the present term following immediate discussion is on-going to support scientific consultations and reviews of PMDA:

1. Drugs
   - **Necessity and condition of placebo-controlled trials for diseases under unmet medical needs**
   - Effective utilization animal models for non-clinical testing to demonstrate POCs
2. Medical Devices
   - Application of numerical analysis for non-clinical testing
   - Evaluation of medical devices for pediatric use (including application of non-clinical testing)
3. Cellular & tissue-based products
   - **Manufacturing and quality of cellular products during the early development in cell processing centers**

Schedule

• November 2013	Promulgation of two laws
• 6 August 2014	Release cabinet and ministerial ordinances
• 12 August 2014 onward	Release guidance notifications: submission, GLP, GCP, GPSP, CT notification, CT AE reports, ADR/Defect reports, Labelling, periodic report, GCTP……
• 25 November 2014	Enactment of two laws

Summery

- In line with the commitment of the administration, Japan is undergoing regulatory reform to support and accelerate R&D of regenerative medicine
- To expedite the access to new promising regenerative medicine in a safe and effective manor
- PMDA will also facilitate R&D by giving scientific/regulatory advice to the sponsors from early stage of development

Future Cooperation

- Information exchange on Japan's requirements on the reformed regulation for regenerative medicine

- Willing to support consideration of Early Access regulation system on regenerative products in Taiwan.

Thank you for your attention

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Literature available in English:

Hara A. Sato D. Sahara Y. New Governmental Regulatory System for Stem Cell–Based Therapies in Japan. ***Therapeutic Innovation & Regulatory Science***. 2014; DOI: 10.1177/2168479014526877