Regulatory Updates on Cellular Therapy Products in Japan

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International Society for Cellular Therapy (ISCT), Auckland, New Zealand

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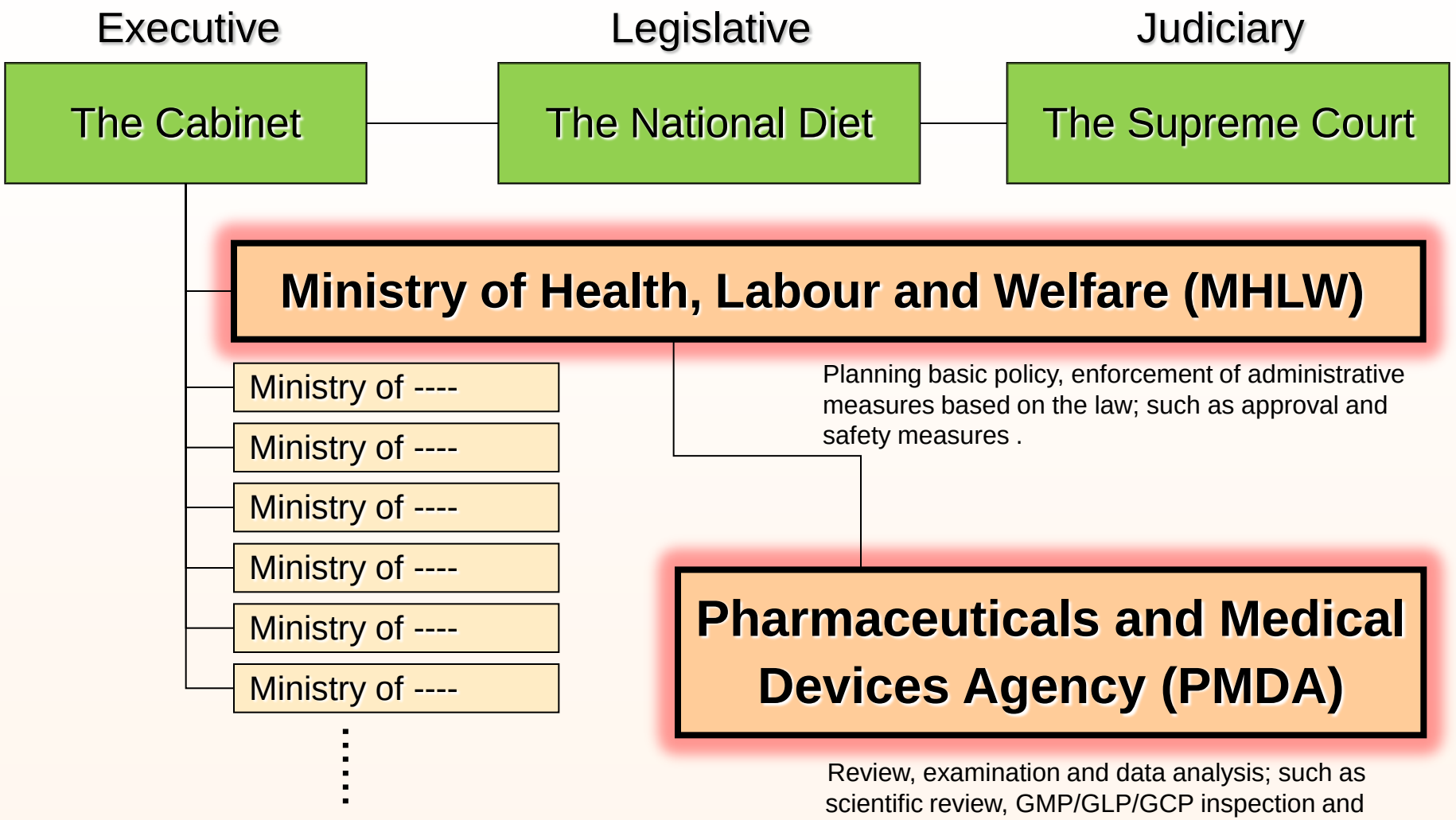
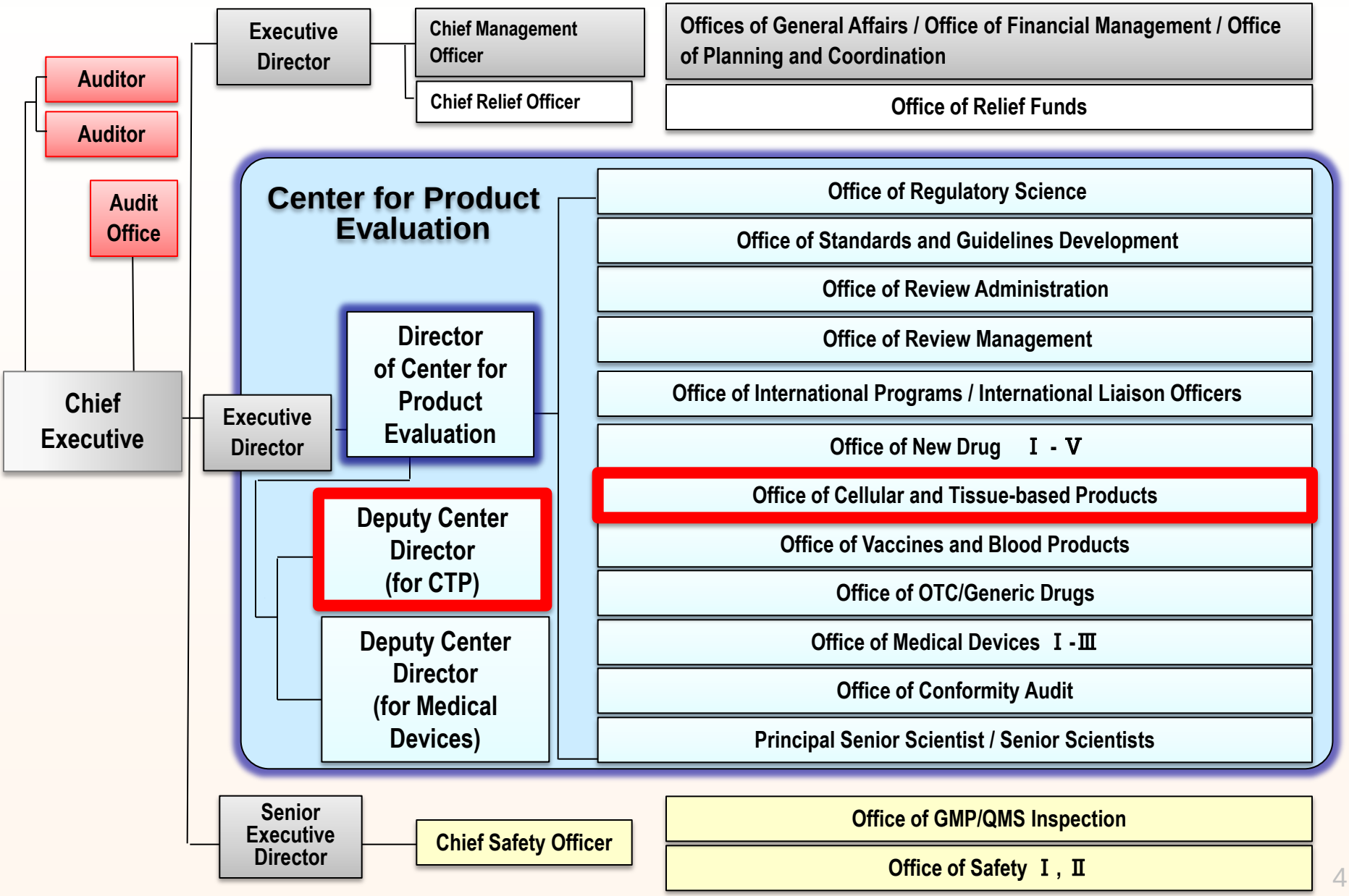
1. Organizational Updates
2. Regulatory Framework for Cellular Therapy Products (CTPs)
3. Future Regulatory Aspects

Japanese Regulatory Bodies



ORGANIZATION OF PMDA AS OF OCT. 2012

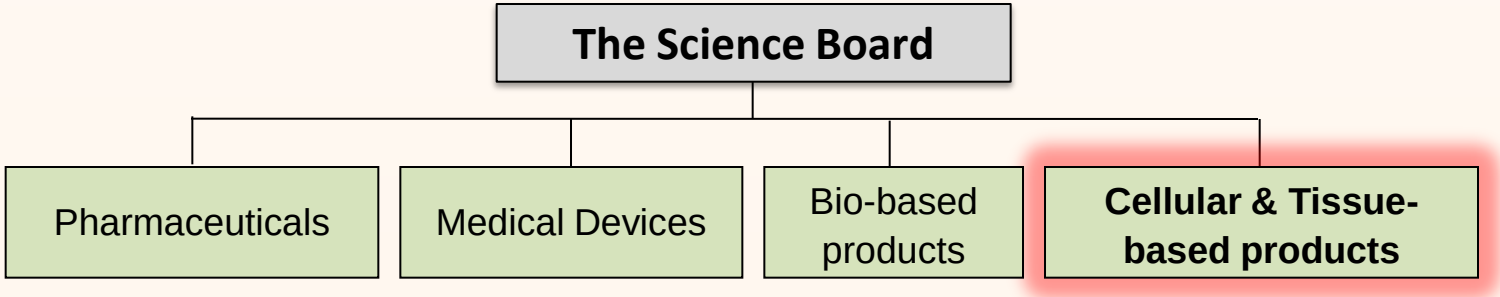


THE SCIENCE BOARD

- PMDA established the Science Board on May 14th 2012, as a high-level consultative body* to advance regulatory science and support PMDA to evaluate products with advanced science and technology.

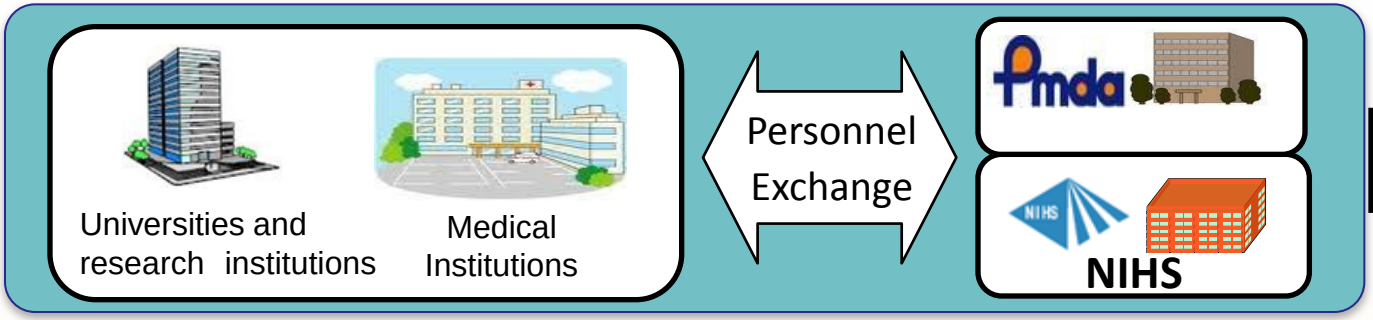
  * Members are external experts from medical, dental, pharmaceutical, engineering and other fields.

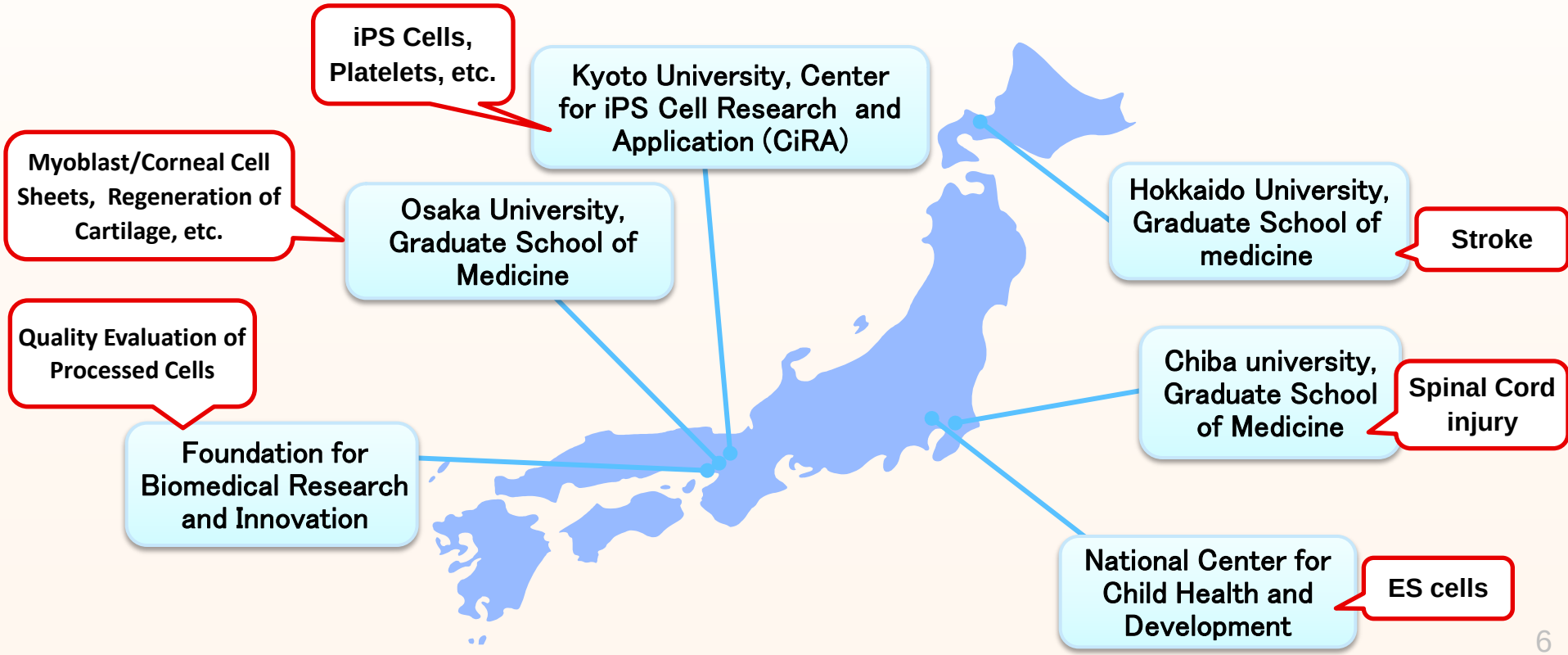
- The Board will make recommendations on review policy for innovative products, development of guidelines, regulatory science research, improvements in the scientific aspects of review.



PROMOTION OF PERSONNEL EXCHANGE

< Program for Cellular Therapy Products >

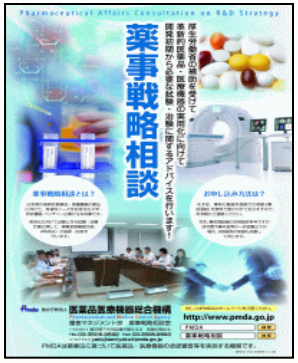




Pharmaceutical Affairs Consultation on R&D Strategy

Valley of Death

- Insufficient knowledge on regulation and development strategy



Basic Research

Pharmaceuticals and Medical Devices candidates

Strategic Consultation

Quality Study

Non-Clinical Study

Clinical Trial

Up to the level of POC studies

Practical Use

Innovative Products

Consultation on quality or toxicity study of biologics, cellular therapy products

Consultation on endpoints or sample size of early clinical trial

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Definition of Cell/Tissue Processing

- Any processing of a cell or tissue with the objective of propagation and/or differentiation of a cell or tissue, cell activation, and production of a cell line, which includes
  - pharmaceutical or chemical treatment,
  - altering a biological characteristic
  - combining with a noncellular component
  - manipulation by genetic engineering.
- The isolation of tissue, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, sterilization by washing or γ-irradiation, freezing, thawing, and such similar procedures regarded as minimal manipulations are NOT considered to be processing.

Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue
(PFSB/MHLW Notifications, 2008)

Drugs or Medical Devices ?

Cellular therapy products will be regulated as Drugs or Medical Devices according to their characteristics.

- Drugs: Pharmacological action*

  * efficacy depends on biological active substances produced from cells

- Medical Devices: Physical or Structural action

<EXAMPLE>

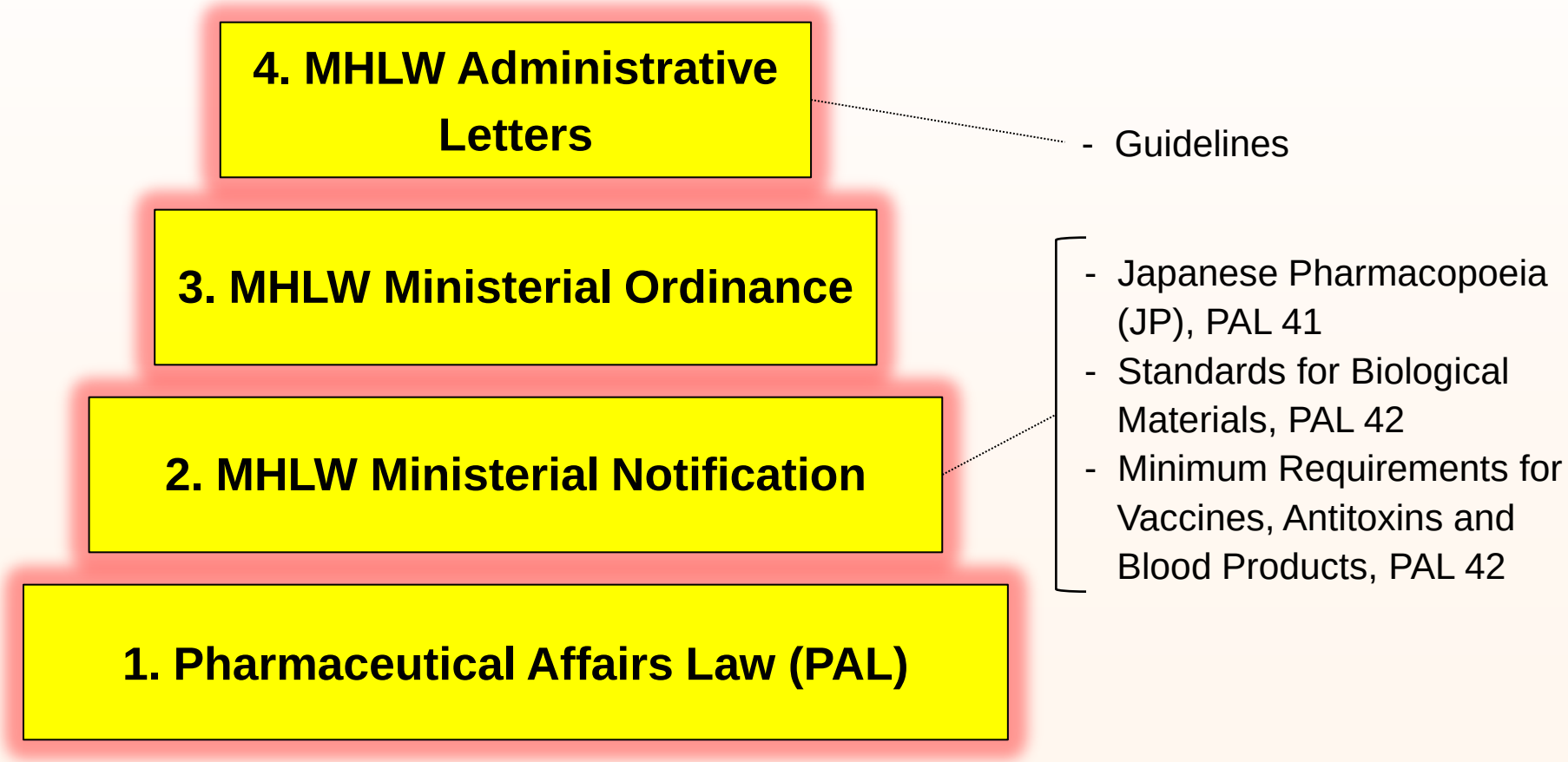
✓ Allogeneic mesenchymal stem cells for GVHD
→ Drugs

✓ Autologous epidermis for burn
→ Medical Devices

✓ Autologous cartilage for traumatic cartilage defects
→ Medical Devices

Regulatory Framework for CTPs

Marketing authorization of Cellular Therapy Products derived from processed human cells/tissues are regulated by the PAL and related regulatory documents.



GUIDELINES FOR CTPS

Good Tissue Practice (GTP)

- Standards for Biological Ingredients (2003)
- General Principles for the Handling and Use of Cellular/Tissue-based Products (2000)

Product 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)

GMP/ QMS

Standards for Manufacturing Control and Quality Control for

- Drugs and Quasi-drugs (2004)
- Medical Devices and In-vitro Diagnostic Reagents (2004)

Standards for Manufacturing Control and Quality Control of Investigational Products (2008)

Points to Consider on Manufacturing and Quality Control of Autologous CTBPs (2008)

Two Tracks for Clinical Study in Japan

	Clinical Trial	Clinical Research
Purpose	Application for Marketing Authorization	Not for Marketing Authorization (advancing medical science and technology)
Regulatory Framework	Pharmaceutical Affairs Law (PAL)	• Medical Practitioners' Act • Ethical GLs for Clinical Research (Ministerial Notification of MHLW No.415, 2008) • GLs for Clinical Research using Human Stem Cells (Ministerial Notification of MHLW No. 425, 2006; Rev., No.380, 2010)
GCP compliance	Mandatory	Not Required
IND-Review	• IRB • PMDA/MHLW	• IRB • MHLW (for researches of stem cell and gene therapy)

CLINICAL TRIALS OF CTPS IN JAPAN

(1) 6 Products (As of July 2012)

	Indication	Cell/Tissue
Auto	Severe heart failure due to chronic ischemic heart disease	Skeletal myoblast
Auto	Focal articular cartilage lesion in the knee	Chondrocyte
Auto	Neurologic manifestation due to cerebral infarction	Mesenchymal Stem Cell
Auto	Giant congenital melanocytic nevus	Epidermal Cell
Auto	Dystrophic epidermolysis bullosa	Epidermal Cell
Allo	Steroid-refractory acute GVHD	Mesenchymal Stem Cell

Auto; Autologous , Allo; Allogenic

Clinical Researches of CTPs in Japan

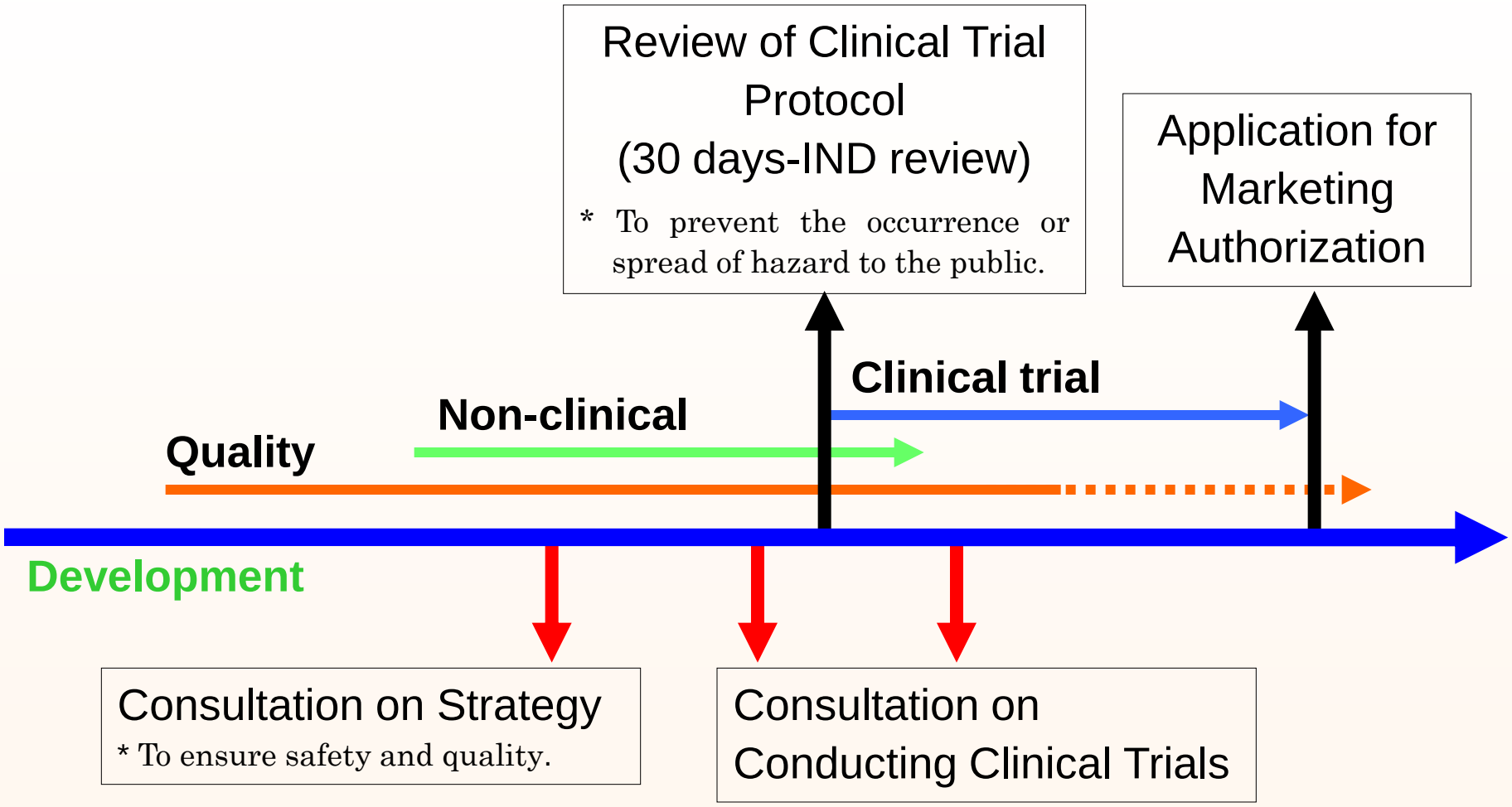
http://www.mhlw.go.jp/bunya/kenkou/iryousaisei06/pdf/111201_4.pdf
http://www.nihs.go.jp/cgtp/cgtp/sec2/sispsc/html/table2.html

(2) 66 Registered* (As of Feb 2013)

*According to Guideline for Clinical Research using Human Stem Cells (No. 425, 2006; Rev., No.380, 2010)

Target Organ	N
Blood Vessel	20
Cornea	9
Bone	8
Periodontium/Dental Pulp	7
Heart	5
Cartilage/Intervertebral Disk	5
Liver	3
Cerebrovascular Disorder	3
Gastrointestinal (GI) Tract	2
Spinal Cord	1
Mamma	1
Urinary System	1
Skin	1

Review of Clinical Trials for CTPs



CTPs Approved for Marketing in Japan (1)

1. Autologous cultured epidermis

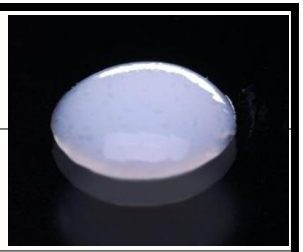
Approval Date	Oct. 29, 2007 (submitted on Oct. 6, 2004)
Target organ	Skin
Brand Name (Company)	JACE (Japan Tissue Engineering Co.,Ltd.)
Notes	Autologous cultured keratinocytes using Green's technique in which keratinocytes derived from the patient's own skin tissue are co-cultured with irradiated 3T3-J2 cells derived from mouse fetuses as a feeder to form a sheet in approximately three to seven layers thick. This is indicated for the treatment of serious large burns that cannot be provided with a sufficient area of donor skin for autologous skin grafting, and of burns in which the total area of deep second-degree (deep dermal) and third-degree (full-thickness) burn is 30% or more of the total body surface area.

http://www.pmda.go.jp/english/service/pdf/list/NewmedicaldevicesFY2007.pdf

CTPs Approved for Marketing in Japan (2)

2. Autologous cultured cartilage

Approval Date	Jul. 27, 2012 (submitted on Aug. 24, 2009)
Target organ	Bone /Cartilage
Brand Name (Company)	JACC (Japan Tissue Engineering Co.,Ltd.)
Notes	An autologous cultured cartilage to alleviate clinical symptoms by implanting it in the affected site of traumatic cartilage eficiency and osteochondritis dissecans (excluding knee osteoarthritis) in knee joints with a cartilage defective area of 4 cm2 or more for which there are no other treatment options. Chondrocytes isolated from the non-load-bearing site of a knee joint of patients by taking a small amount of cartilage tissue are three-dimensionally cultured in atelocollagen gel to obtain this product. Clinical studies were conducted to evaluate the efficacy and safety of this product for patients with traumatic cartilage deficiency, osteochondritis dissecans, and knee osteoarthritis.



http://www.pmda.go.jp/english/service/pdf/list/NewmedicaldevicesFY2012.pdf

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Outsourcing of processing of Cell/Tissue

Draft Under Consideration

Clinical Research/Medical Practice

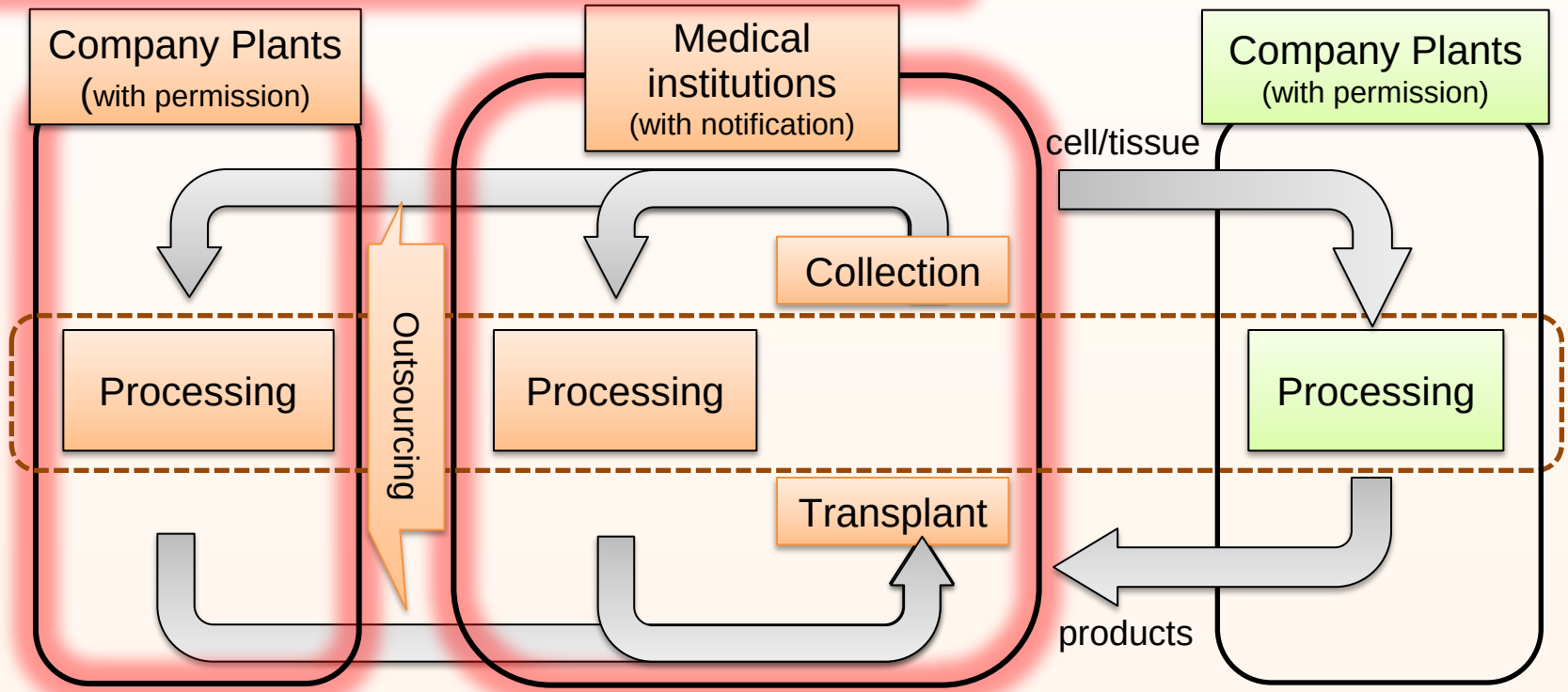
New Regenerative Medicine Law

To ensure safety of regenerative medicine by stipulating standards for medical facilities and processing/manipulation plants

Marketing Authorization

Pharmaceutical Affairs Law

To ensure efficacy and safety of marketing products by stipulating manufacturing standards



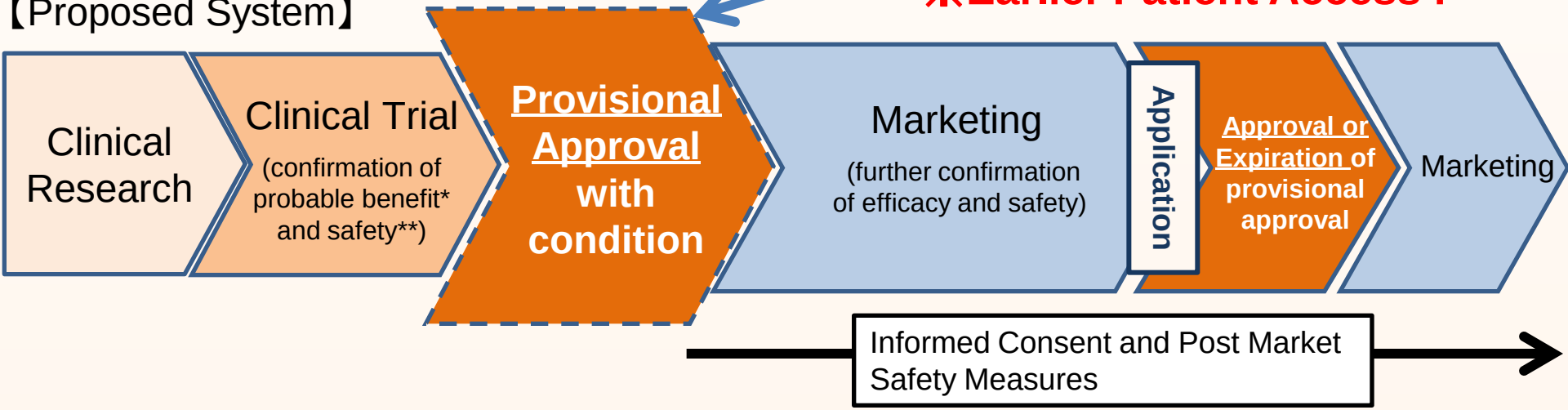
NEW APPROVAL SYSTEM FOR COMMERCIALIZATION OF CELLULAR THERAPY PRODUCTS

Draft Under Consideration

【Current System】

【Proposed System】

※Earlier Patient Access !



* Probable benefit: Confirmation of efficacy with small patient population.
** Safety: Earlier detection and evaluation of adverse events.

Thank you for your attention!

PMDA strongly supports the development of innovative products