Regulatory Updates on Cellular and Tissue-based Products in Japan

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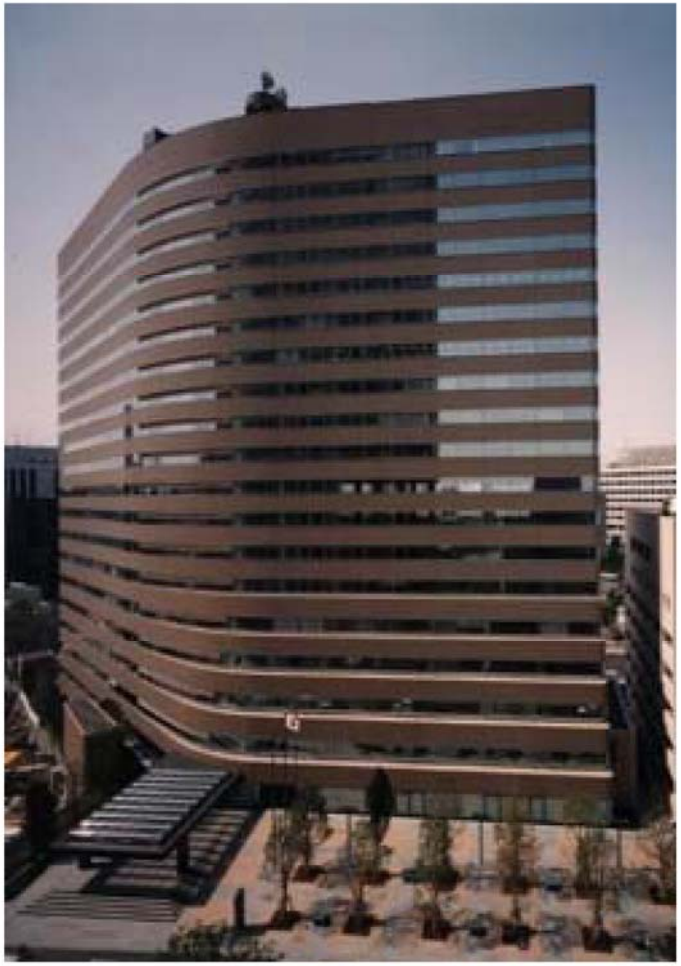
Disclaimer:
The views and opinions expressed in this presentation are those of the presenter and should not necessarily represent the views and opinions of the PMDA.

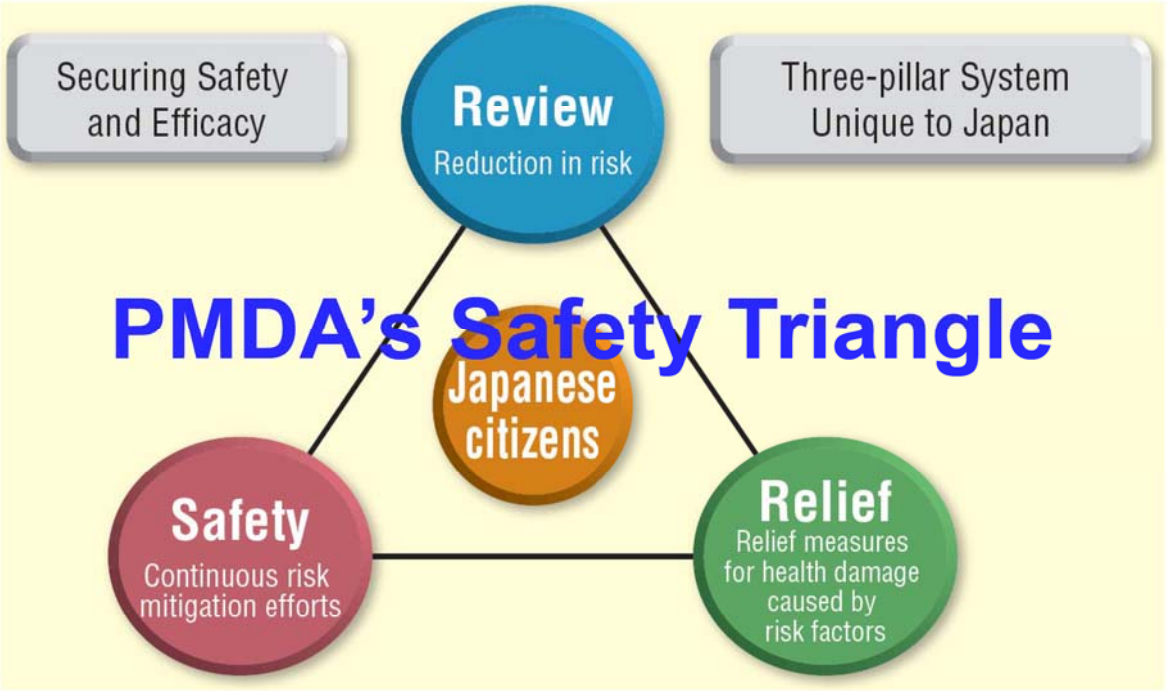
Introduction of PMDA



Tokyo, JAPAN

Pharmaceuticals and Medical Devices Agency (PMDA)

- an Incorporated Administrative Agency (IAA)



Two Japanese Regulatory Authorities

- **Ministry of Health, Labor and Welfare (MHLW)**

  Planning basic policy, enforcement of administrative measures based on the law

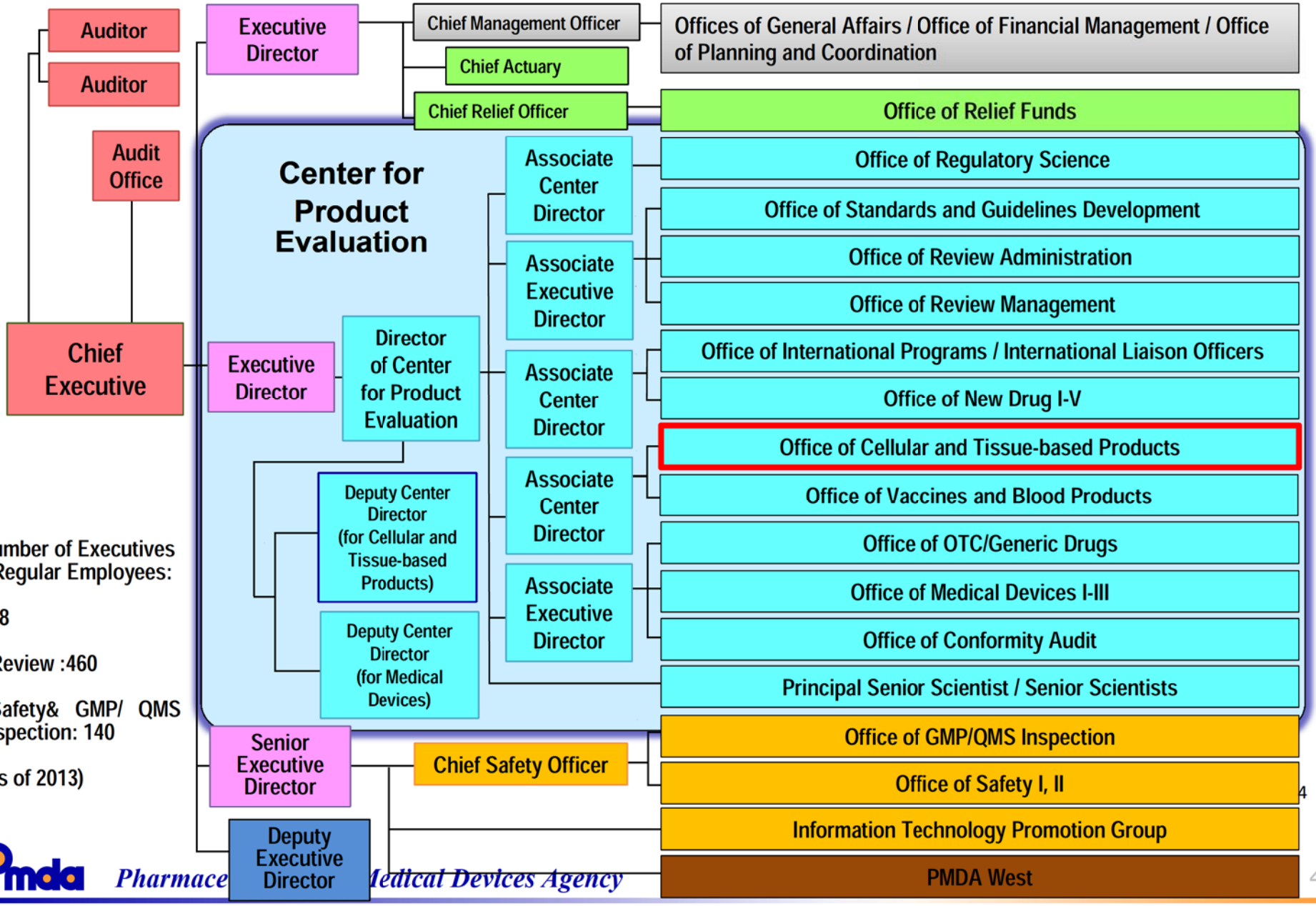
  - Marketing authorization of pharmaceuticals and medical devices
  - Issue emergency safety information and direct product withdrawal
  - Safety measures for emergent and significant cases

- **Pharmaceuticals and Medical Devices Agency (PMDA)**

  Review, examination and data analysis

  - Scientific review, GMP/GLP/GCP inspection and consultation on the development of pharmaceuticals and medical devices for marketing authorization
  - Collection, analysis and dissemination of information relating to quality, efficacy and safety of pharmaceuticals and medical devices

Organization of PMDA



Number of Executives &Regular Employees:

708

・Review :460

・Safety& GMP/ QMS inspection: 140

(As of 2013)

Today's Topics

1. Guidelines for Cellular and Tissue-based Products(CTBPs) and Recent Discussion on Safety Issues
2. New Regulatory Framework for CTBPs in Japan

1-1. Guidelines for CTBPs

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 cells

- 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 Consider 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)

・Allogenic induced pluripotent stem cells-derived retinal pigment epithelial cells (Draft)

Good Tissue Practice (GTP) /GMP/QMS

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

Standards for Biological Ingredients (2003)

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)

1-2. Outline of "Guidelines on Ensuring the Quality and Safety of Products Derived from Processing of Allogenic Human iPS(-Like) cells"(1)

Chapter 1 General Consideration

1. Purpose
2. Definitions

Chapter 2 Manufacture

1. Source Materials
2. Manufacturing Process
3. Quality Control of Final Product

Chapter 3 Stability

Chapter 4 Non-Clinical Safety Study

Chapter 5 Studies to Support Efficacy/Performance of Products

Chapter 6 Biodistribution/Localization

Chapter 7 Clinical Study

Outline of "Guidelines on Ensuring the Quality and Safety of Products Derived from Processing of Allogenic Human iPS(-Like) cells"(2)

Chapter 4 Non-Clinical Safety Study

Examples of points to consider, when confirming the preclinical safety of a products:

1. Inadvertent transformation & abnormal proliferation of non-target cells
2. Effect of active substances including cytokines and growth factors produced by the cells
3. Potential effects on the normal cells/ tissues, and their consequences
4. Possibility of the formation of ectopic tissue

Outline of "Guidelines on Ensuring the Quality and Safety of Products Derived from Processing of Allogenic Human iPS(-Like) cells"(3)

Chapter 4 Non-Clinical Safety Study

5. Undesirable immunological reactions due to the product and/or expression of transgene
6. Tumorigenicity
7. Residue of exogenous gene, insertional mutagenesis
8. General toxicity studies

Consider in a comprehensive manner, taking into account
the characteristics of the product,
the route of administration, target diseases, etc.

1-3. Clinical Research of iPS Cells derived Product

< Two Tracks for Clinical Study >

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

Health Science Council's points to iPSC-derived retinal pigment epithelium (RPE) cells for wet-type AMD (1)

Quality and Non-clinical Issues

- Tumorigenicity
- Safety for the plasmid (EB virus-based episomal plasmid vector) used for gene transduction
- Genomic instability
- *In vitro* viral testing

http://www.mhlw.go.jp/file.jsp?id=145046&name=2r98520000036x94.pdf
(Japanese only)

Health Science Council's points to iPSC-derived retinal pigment epithelium (RPE) cells for wet-type AMD(2)

Clinical Issues

- Monitoring;
  - Long term follow up for tumorigenicity
- Complicating factors for evaluation;
  - Simultaneous surgery for cataract
  - Combined therapy with anti-VEGF antibody after transplantation
- Contents of IC document

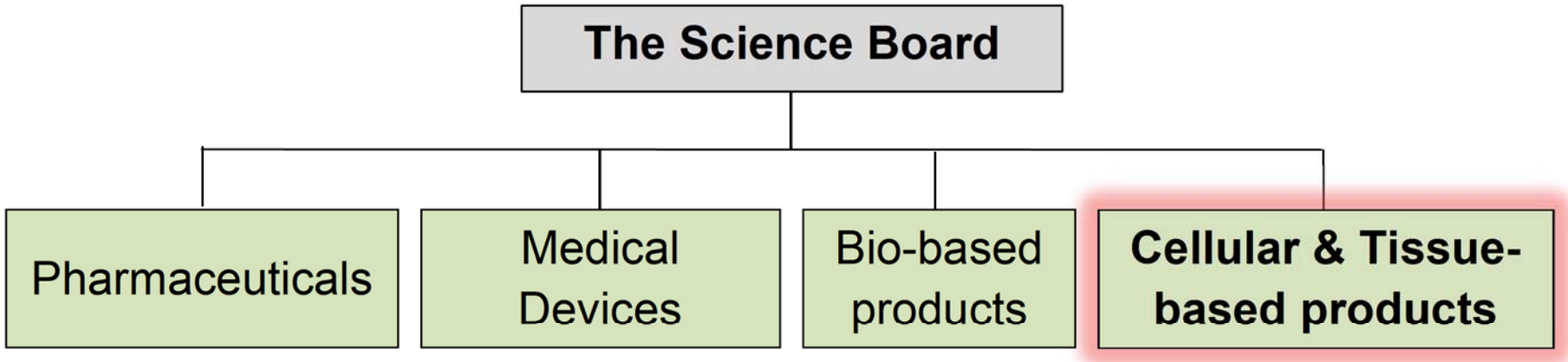
http://www.mhlw.go.jp/file.jsp?id=145046&name=2r98520000036x94.pdf
(Japanese only)

1-4. The Science Board (PMDA)

- 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 made by advanced science and technology.

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

- The Board makes recommendations on reviewing policy and developing guidelines for innovative products from the scientific aspects of review.



"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" (1)

- August 20, 2013, Cellular and Tissue-based Products Subcommittee -

http://www.pmda.go.jp/english/scienceboard/scienceboard/pdf/20130820/file01.pdf

- This report presents a summary of the scientific point of view on the development of CTBPs, and not direct requirements for regulatory approval.
- The correlation between tumorigenicity of the (stem) cells used for manufacturing and that of the final product has not been elucidate.
- Main concerns on iPSCs

(1) "Genetic abnormality that induces persistent cell proliferation"

- Detection of residual exogenous pluripotency-inducing transgenes
- Confirmation of karyotype and abnormality in DNA sequences of all exons

(2) "Genomic instability"

- Confirmation of the genomic mutation rate after iPSCs are cultured

"Current Perspective on Evaluation of Tumorigenicity of CTBPs Derived from iPSCs and iPSCs as Their Starting Materials" (2)

- Detection methods for malignant transformation;
  - (1) Soft agar colony formation assay
  - (2) Focus formation assay
  - (3) Growth factor-independent growth assay
  - (4) Tumorigenicity test using nude mice (WHO TRS878)
    - These methods were originally intended to be used for a characterization of a relatively homogeneous cell population, such as cell line or cell bank.
    - Sufficient sensitivity for detection of a very small number of tumorigenic cells?
    - Extrapolability for human use?
- Tumorigenicity test by subcutaneous transplantation to severely immunodeficient mice, such as NOG or NSG mice
- For each final product, it is necessary to assess a practically safe level of tumorigenic cell contamination, establish a test method that can detect it, and then determine a cut-off value.

"Current Perspective on Evaluation of Tumorigenicity of CTBPs Derived from iPSCs and iPSCs as Their Starting Materials" (3)

- Consensus;
  - The present scientific technology cannot completely eliminate the risk of tumorigenicity of CTBPs derived from iPSCs
  - Efforts should be made to make use of the means available at present to a reasonable extent, and to reduce the risk as much as possible
- To select suitable tests based on the properties of each final product and to perform follow-up studies as long as possible should be considered.

- This report presents a summary of the scientific point of view on the development of CTBPs, and not direct requirements for regulatory approval.

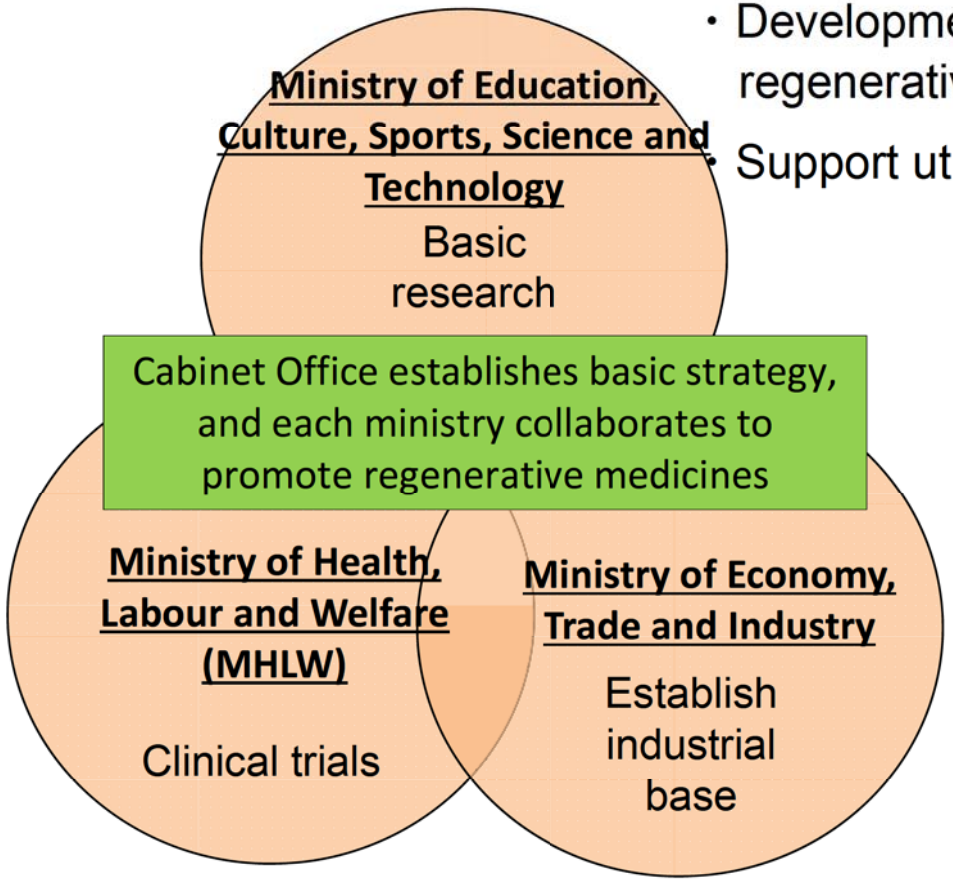
Today's Topics

1. Guidelines for Cellular and Tissue-based Products(CTBPs) and Recent Discussion on Safety Issues
2. New Regulatory Framework for CTBPs in Japan

2-1. Government's Policy:

Regenerative Medicine Promotion Law (Enacted in May 2013)

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



Goals for the next 7 years

- To apply new drugs developed by iPS cell technology to clinical trials
- To increase the number of approved cellular therapeutic products
- To expand the target diseases in clinical trials
- To develop equipment or devices related to regenerative medicine

→2 Acts have been passed the Diet in Nov. 2013

2-2. 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

2-3. The Act on Pharmaceuticals and Medical Devices (PMD Act)

◆ Background of additions for regenerative medical products

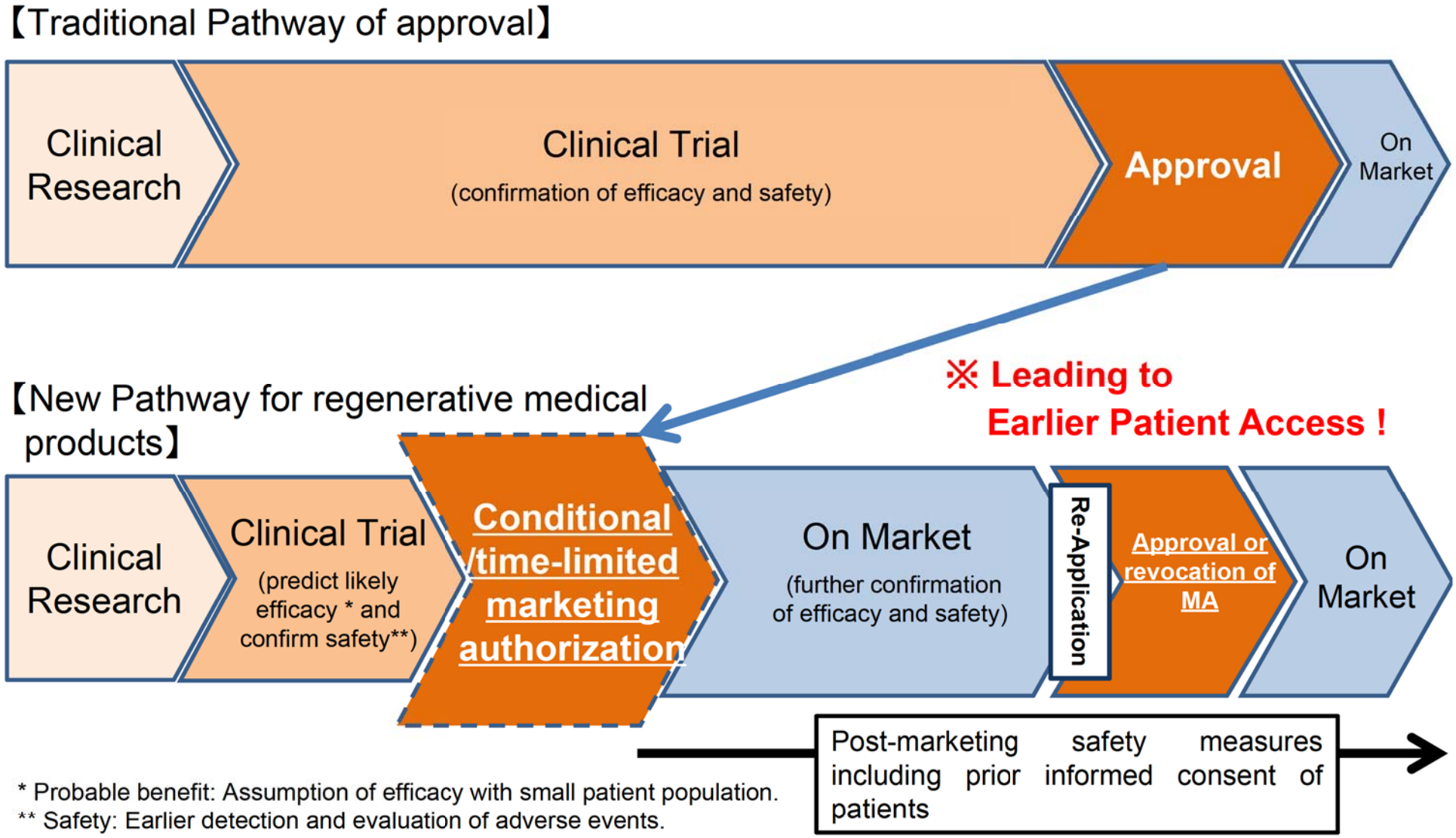
Difficult to gather and evaluate the data for efficacy of regenerative medical products in a short time due to heterogeneity of cells

→ To secure timely provision of safe regenerative medicines, a new 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.

2-4. New Marketing Authorization in PMD Act



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

For more information, Please visit the PMDA website

http://www.pmda.go.jp

http://www.pmda.go.jp/english/index.html(←English)

Take-home messages

- Pre-clinical safety studies for CTBPs should be designed on a case-by-case basis taking into account their characteristics.
- The Science Board of PMDA have scientifically discussed on the tumorigenicity of CTBPs derived from pluripotent stem cells.
- New regulations suitable for CTBPs are now being enforced in Japan to secure their safety and to accelerate their marketing.
- PMDA encourages active use of consultations from the early stages of development.

Thank you for your attention!