Japan's Regulations on Regenerative Medicine

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JAPAN

Review Process for Marketing Authorization (1/2)

Pharmaceuticals and Medical Devices Agency (PMDA)

Review, examination and data analysis

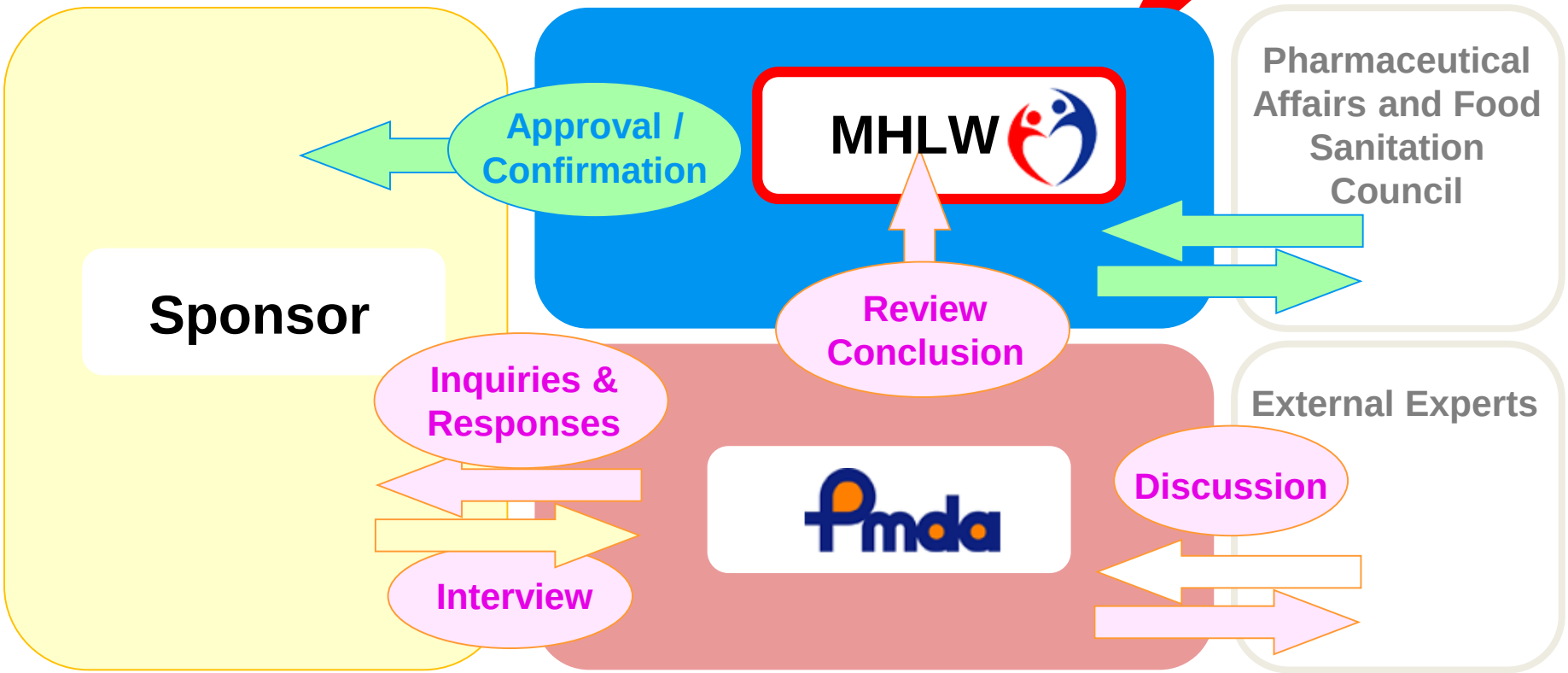
- Scientific review, GMP/GLP/GCP inspection and consultation
- Collection, analysis and dissemination of information relating to quality, efficacy and safety of pharmaceuticals and medical devices

Review Process for Marketing Authorization (2/2)

Ministry of Health, Labor and Welfare (MHLW)

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

- Marketing authorization
- Issue emergency safety information and direct product withdrawal/recall
- Safety measures for emergent and significant cases



Outline

- **New Regulatory Systems**
  - ✓ The Act on the Safety of Regenerative Medicine
  - ✓ The Pharmaceuticals, Medical Devices and Other Therapeutics Products Act (PMD Act)

- **Consultation and Review Pathway for Regenerative Medical Products**
  - ✓ Conditional and Time-Limited Authorization
  - ✓ Pharmaceutical Affairs Consultations on R&D strategy
    (New Name; Regulatory Science Strategy Consultations)

- **SAKIGAKE Designation System**

Tow Tracks for Regenerative Medicine in Japan

Clinical Study

Clinical Research

Medical Care

Clinical Trials

- Sponsor initiated Clinical Trials
- Investigator initiated Clinical Trials

Not for Marketing Authorization

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

Handled by MHLW

Marketing Authorization Purpose

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

Handled by MHLW & PMDA

Background for New Legislations

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

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

Not for Marketing Authorization

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

Marketing Authorization Purpose

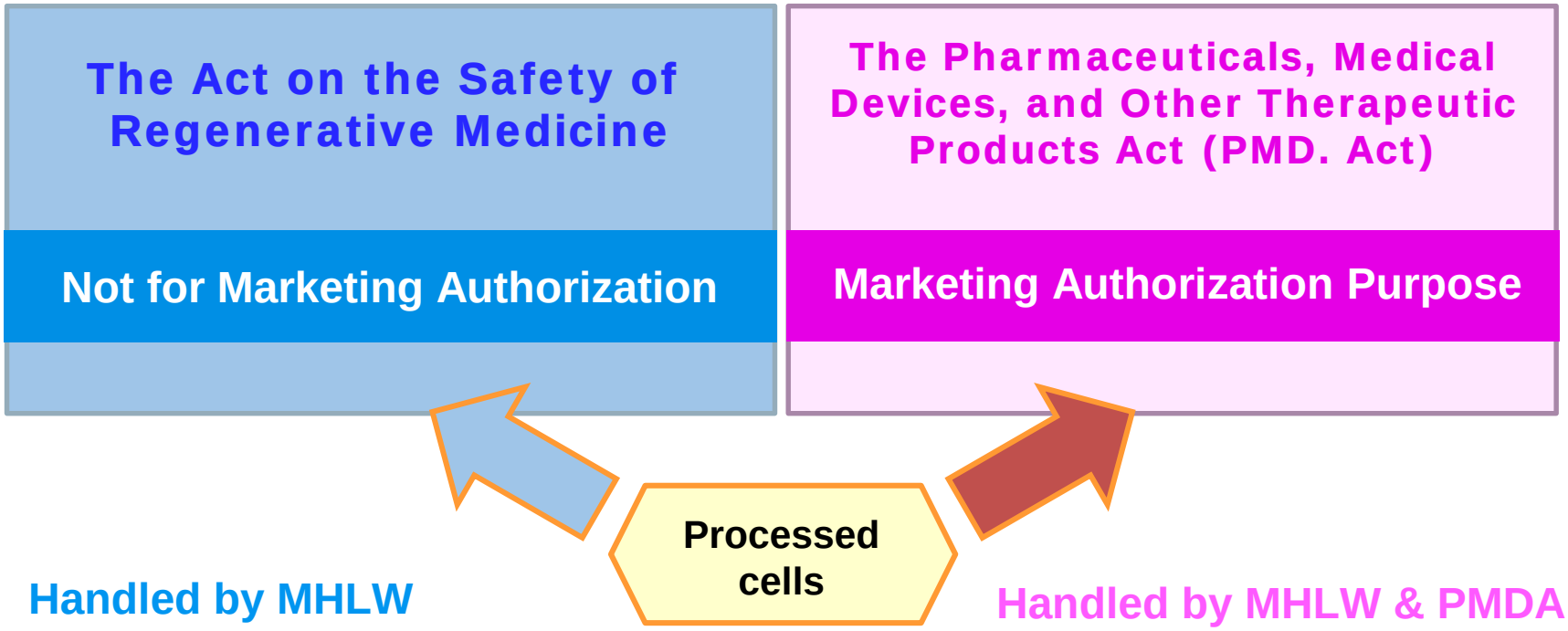
✓ Production and marketing of regenerative and cellular therapeutic **products** by firms

Revision of the previous system was needed.

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.

These two acts were enacted on 25 November 2014



Act on the Safety of Regenerative Medicine

I. Obligate hospitals and clinics to submit provisional plans of regenerative medicine

MHLW

Certified committee for regenerative medicine

Hospitals / Clinics

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

II. Enable commissioning cell processing to licensed enterprises

Cell Processing

III. Obligate CPCs to notify or obtain license

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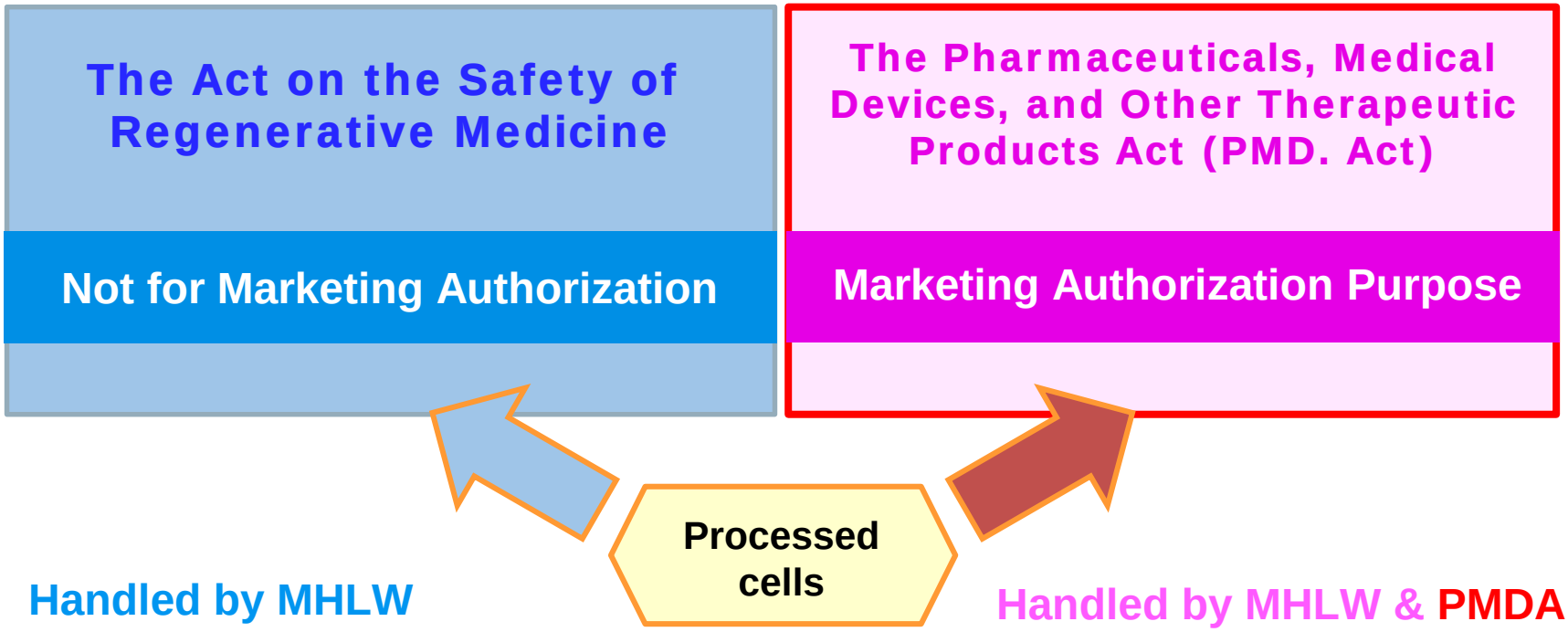

Regenerative Medical Products in the PMD Act

◆ Additions for Regenerative Medical Products

① **Definition and independent chapter for Regenerative Medical Products**

② Introduction of conditional/time limited approval system

Drug	**Regenerative Medical Products**	Device

Definition

Regenerative medical products are defined as **processed live human/animal 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 disease, or
2) for gene therapy.

Cellular and Tissue based Products and Gene therapy Products

Scope of Manipulation (“Processed cells”) to be

Manipulation to be regulated

- Any processing of a cell or tissue with the aim of treating a patient, repairing or regenerating tissue, which includes
  - propagation / differentiation of cells or tissues,
  - production of a cell line,
  - pharmaceutical or chemical treatment to activate cells,
  - altering a biological characteristic,
  - combining with a non-cellular component,
  - manipulation by genetic engineering.

Manipulation not to be regulated

- Those procedures are regarded as minimal manipulations and NOT considered to be processing.
  - Isolation / disintegration / separation of tissues
  - isolation of specific cells
  - treatment with antibiotics
  - sterilization by washing or g-irradiation

Blood transfusion, Hematopoietic stem cell transplantation etc. are excluded from the scope of the regenerative medicine regulation.

How to expedite R&D and review (1/2)

◆ Additions for Regenerative Medical Products

1. Definition and independent chapter for Regenerative Medical Products
2. **Introduction of *Conditional and time limited marketing authorization***

Limitations of Clinical Trials of Regenerative Medicine to satisfy unmet medical needs

◆ Designed for unmet needs under the present treatment (e.g. last line therapy): limited number of patients available for clinical trials

◆ Difficult to conduct controlled study to demonstrate clinical benefit, in the Japanese medical environment, due to:

- highly invasive surgical intervention
- autologous cell collection

◆ Clinical trial design affected by heterogeneity of quality derived from source materials (including autologous collection and culture procedures)

How to expedite R&D and review (2/2)

◆ Additions for Regenerative Medical Products

1. Definition and independent chapter for Regenerative Medical Products
2. **Introduction of *Conditional and time limited marketing authorization***

✓ **Difficult to gather and evaluate the data for efficacy of regenerative medical products**

⇒ To secure timely provision of safe regenerative medicines: a new regulatory frame work is needed.

Expedited approval system for regenerative medical products

After the safety is confirmed and the results predict likely efficacy, the products will be given conditional, time-limited marketing authorization.

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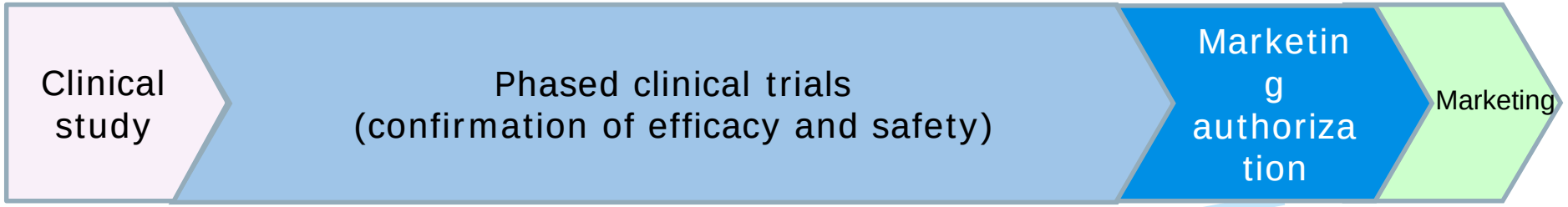
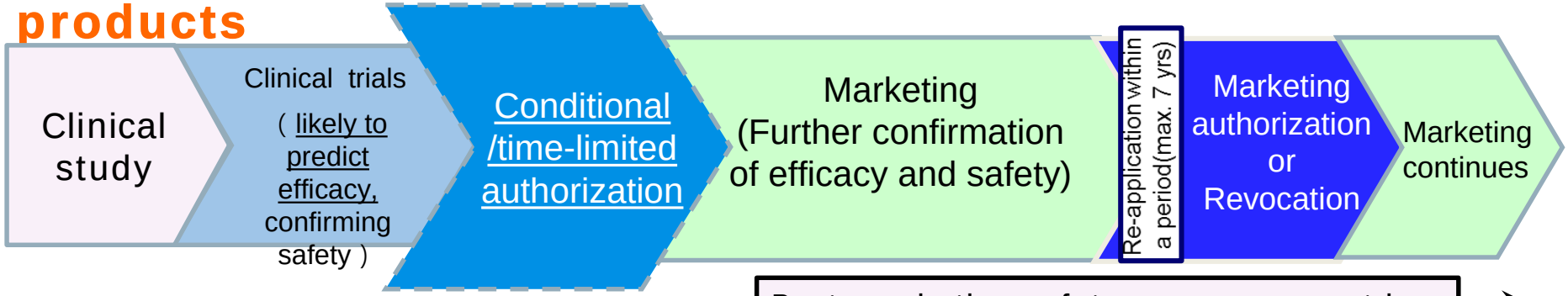
Expedited approval system under the PMD Act

< 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 scheme

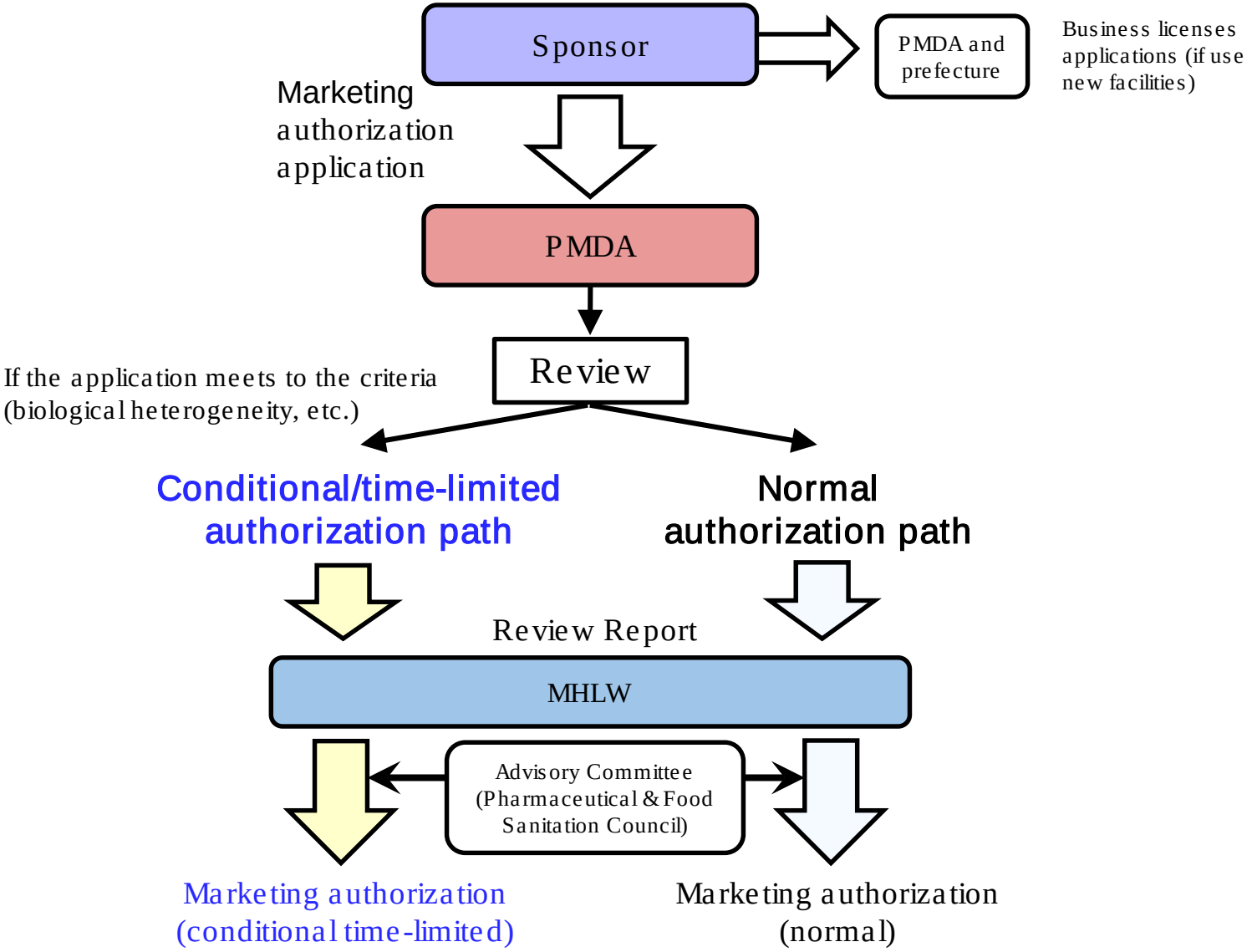


New scheme for regenerative medical products



Post-marketing safety measures must be taken, including prior informed consent of risk to patients

Review Pathway of Regenerative Medical Products



New Products Approved under New Regulatory Framework

Bone marrow mesenchymal stem cells (MSCs) : *Temcell HS inj.*

- ✓ For acute Grafts versus Host Disease (aGVHD)
- ✓ Allogeneic MSC

JCR

Normal authorization

Skeletal myoblast derived cell sheet : *HeartSheet*

- ✓ For serious heart failure due to ischemic heart disease
- ✓ Autologous myoblast cells

TERUMO

Conditional and time-limited authorization

Two authorized products under Pharmaceutical Affairs Law

J-TEC

- Autologous Culture Epidermis ***JACE***
- Autologous Cultured Cartilage ***JACC***

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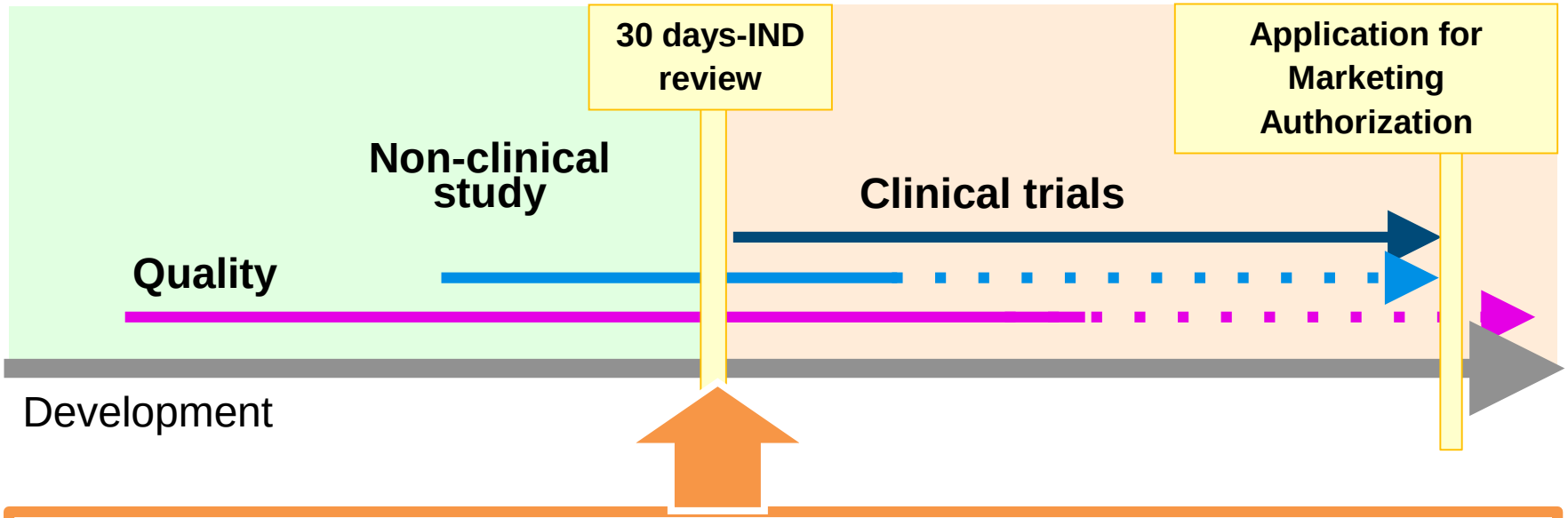
Consultation and Review Pathway



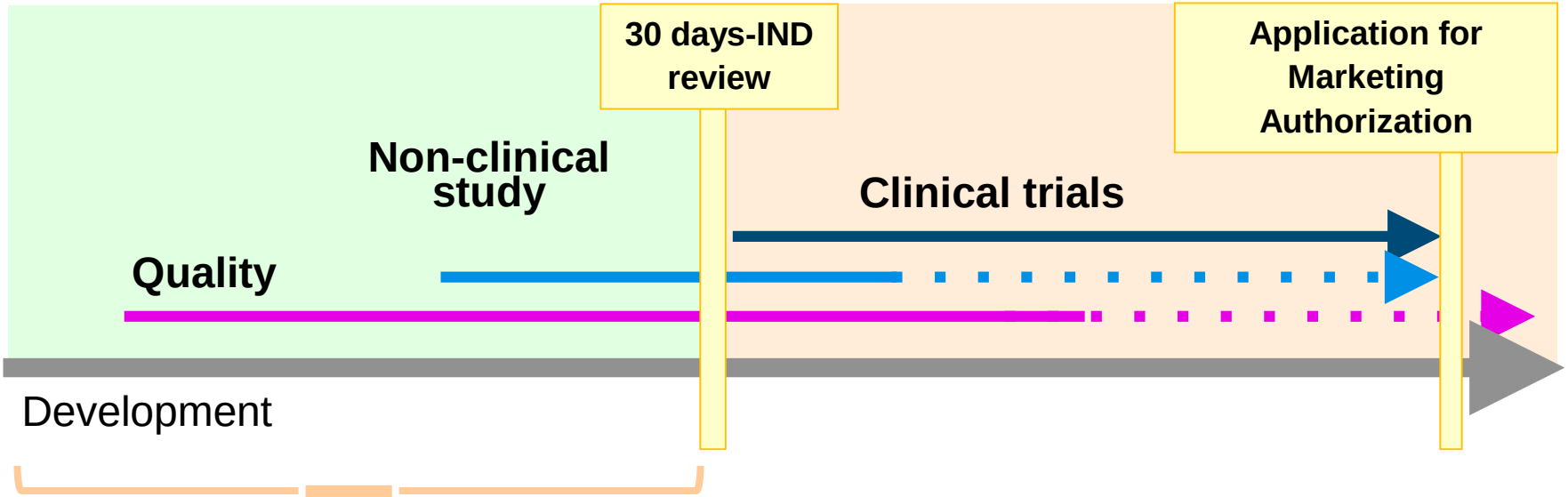
Purpose of 30-days IND Review :

To prevent the occurrence or spread of hazard to the public

- ✓ Regenerative Medicine is a new technology and well-defined methodology has not yet been established
- ✓ Minimize infection risk because virus inactivation on cell products is impossible
- ✓ Cell products may persist in the body for an extended period

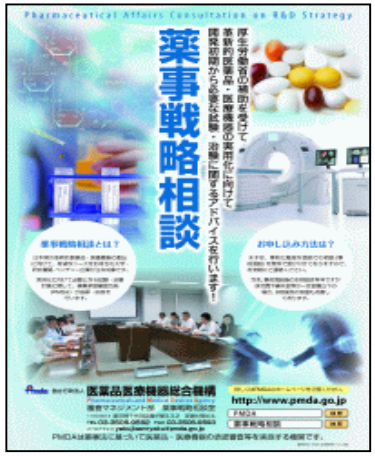
▶ The quality and safety have to be evaluated before starting Clinical trials.

Consultation and Review Pathway



Pharmaceutical affairs consultation on R&D strategy

- Consultations on quality and safety of pre-clinical
- Consultations on clinical trials (up to POC studies)

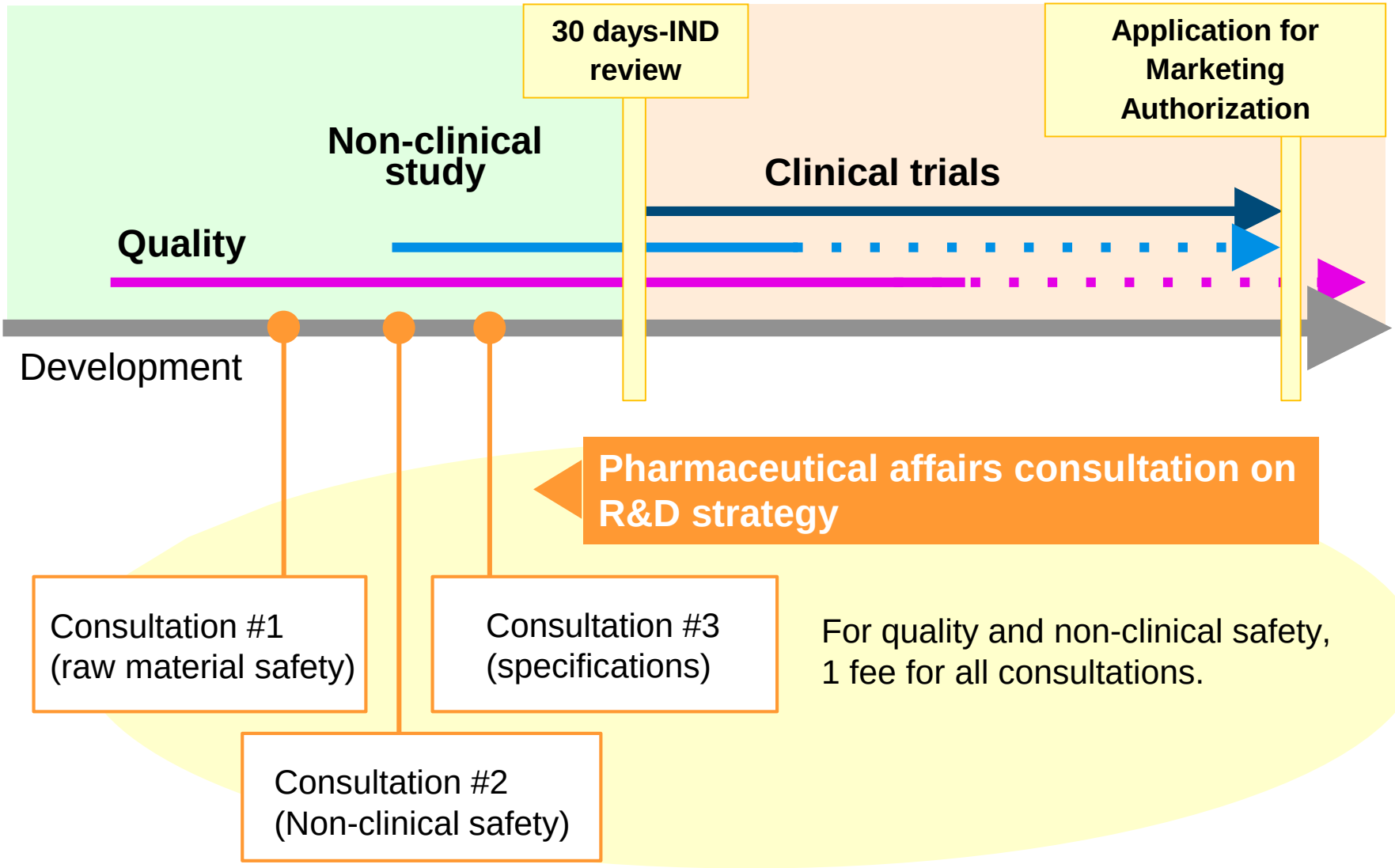


Points of Consultation on R&D Strategy

- **Examples of Quality Questions**
  - Source materials (donor selection criteria and eligibility)
  - Other bio materials safety (raw material standards)
  - Characterization and specification
  - In process control …etc.
- **Examples of Pre-clinical Questions**
  - General toxicity study
  - Tumorigenicity
  - Safety of Manufacturing process derived impurities

To complete IND review in 30 days, these issues have to be resolved in consultations in advance.

Consultation and Review Pathway



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Strategy of SAKIGAKE (Forerunner review assignment system)

厚生労働省
Ministry of Health, Labour and Welfare

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Strategy of SAKIGAKE

(Japanese)

The Ministry of Health, Labour and Welfare (MHLW) has formed the "Strategy of SAKIGAKE" by Ministry Project Team to lead the world in the practical application of innovative medical products (Press release (in Japanese) This PT has been launched to plan strategies as a package covering from basic research to the practical application with related divisions within the MHLW.

The Strategy of SAKIGAKE consists of two measurements as follows and covers from basic research to clinical research/trials, approval reviews, safety measures, insurance coverage, improvement of infrastructure and the environment for corporate activities, and global expansion.

- SAKIGAKE Designation System: promoting R&D in Japan aiming at early practical application for innovative pharmaceutical products, medical devices, and regenerative medicines.
- Scheme for Rapid Authorization of Unapproved Drugs: accelerating the practical application of unapproved/off-label use of drugs for serious and life-threatening diseases by expanding the scope of the Council on Unapproved Drugs/Off-label Use to include unapproved in Western countries if it satisfies certain conditions and by improving the environment for companies to undertake development of such drugs.

The MHLW will implement these policies during the budgetary request process in FY2015, but some of them which are ready will be executed in 2014 ahead of schedule.

MHLW drew up a new strategy to lead the world in the practical application of innovative medical products in 2014.

General Timeframe of Forerunner Review System